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Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R15NS088776
St. Mary's College of Maryland

Title: Neuronal deletion of phosphatase and tensin homolog in mice results in spatial dysregulation of adult hippocampal neurogenesis

Authors: *S. LATCHNEY[1], **B. RUIZ LOPEZ**[1], P. D. WOMBLE[2], K. BLANDIN[2], J. N. LUGO, Jr.[2];
[1]Dept. of Biol., St. Mary's Col. of Maryland, St. Mary's City, MD; [2]Dept. of Psychology, Baylor Univ., Waco, TX

Abstract: Neurogenesis is a multistep process that is involved in hippocampal-dependent cognition and behavior. The tumor suppressor gene phosphatase and tensin homolog deleted on chromosome ten *(Pten)* has previously been found to restrict the proliferation of neural stem/progenitor cells (NSPC) *in vivo*. In this study, we aimed to provide a comprehensive picture of how conditional deletion of *Pten* may regulate the genesis of NSPCs in the adult hippocampal dentate gyrus and subventricular zone lining the lateral ventricles, using gold-standard markers and quantification of the neurogenesis process. We quantified proliferating cells (Ki67+), neuroblasts/immature neurons (doublecortin [DCX+]), and apoptotic (cleaved caspase-3 [CC3+]) cells via stereology in dentate gyrus subregions (subgranular zone [SGZ], outer granule cell layer [oGCL], molecular layer, and hilus) in male and female mice at 4 weeks (N=6 each) and 10 weeks (N=5-6 each) of age. Our data demonstrate that conditional deletion of *Pten* in mice results in a transient and sequential increase in Ki67+ proliferating cells and DCX+ postmitotic neurons in the dentate gyrus, particularly in males. Specifically, we found that conditional *Pten* deletion in males initially increased Ki67+ cell number by 64% in the neurogenic SGZ at 4 weeks of age. These increases were not observed in female $Pten^{-/-}$ mice. However, by 10 weeks of age, the increase in Ki67+ cells spread to non-neurogenic dentate gyrus areas, including the hilus (988% increase), oGCL (273% increase), and molecular layer (150% increase). We also observed a transient increase (98% increase) in DCX+ neurons in male, but not female, $Pten^{-/-}$ mice at 10 weeks of age. In contrast, quantification of Ki67+ cells in the subventricular zone lining the lateral ventricles revealed a 53% decrease in $Pten^{-/-}$ mice compared to wild-type mice at 10 weeks of age. Together, our results demonstrate that loss of *Pten* results in age-, sex-, brain-region dependent increases in adult neurogenesis. Our work is consistent with the literature showing that *Pten* serves as a negative regulator of dentate gyrus neurogenesis but adds temporal and spatial components to the existing knowledge.

Disclosures: **S. Latchney:** None. **B. Ruiz Lopez:** None. **P.D. Womble:** None. **K. Blandin:** None. **J.N. Lugo:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Title: Importance of thyroid hormones T3 for the development and activity of GnRH reproductive neurons

Authors: *C. QUIGNON[1], A. BACKER[2], H. BOW[2], S. WRAY[2];
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Abstract: Clinical studies have shown that thyroid disorders and alteration of thyroid hormone production by environmental endocrine disruptors (EDCs), have deleterious effects on reproduction. By acting in the brain on the hypothalamic component of the reproductive axis, abnormal levels of thyroid hormones can disturb sex hormones production, oestrus cycles or puberty onset, possibly leading to subfertility. Moreover, in animal models, endocrine disruptors and thyroid hormones have been shown to have long-lasting transgenerational effects with the maternal hormones influencing the development of foetal reproductive functions. Despite clear evidence of an interaction between the thyroid and reproductive systems, the effect of T3, the active form of thyroid hormones, on the GnRH neurons controlling reproduction, have been poorly studied. In this work we investigated how T3 functionally interacts with GnRH neurons and how abnormal concentration of T3 alters the migration of these neurons during development. Calcium imaging was used to study the direct effect of T3 on GnRH neuronal activity in an *ex vivo* nasal explants model. Acute administration of T3 was found to stimulate the activity of GnRH cells. Dual labelling of GnRH and thyroid hormone receptors (TR) showed that the GnRH neurons express both nuclear and membrane receptors. However, the use of an antagonist specifically blocking the TR nuclear receptors (1-850), didn't inhibit the T3 stimulatory effect while blockage of integrin αV/β3 membrane receptors (with cilengitide), prevented the T3-induced increase in GnRH neuronal activity. During development GnRH neurons migrate from the nasal placodes into the brain. We found that a 24hr treatment with T3 significatively increased the migration rate of the GnRH neurons in our *ex vivo* model. To assess the transgenerational effect of thyroid disruption on the development of reproductive axis, pregnant females mice have been treated with methimazole (MMI) during gestation to induce hypothyroidism. In E13 embryos, treatment with MMI didn't affect the distribution of the GnRH neurons along the migration tracks but it significantly decreased the general amount of GnRH neurons. Other stages of embryonic development will be studied to investigate this effect. Together these studies are the first to report a direct effect of thyroid hormones on GnRH neuronal activity, through the integrin αV/β3 membrane receptors and show that T3 can modulate the migration of GnRH neurons during development. These results will bring new

insights on how thyroid disruption by EDCs or thyroid diseases, especially during foetal development, can lead to long term reproductive defects.

Disclosures: **C. Quignon:** None. **A. Backer:** None. **H. Bow:** None. **S. Wray:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01MH132089-01
R01-NS120667
R01-NS08389
R01-NS110388
DST Spark Grant

Title: Radial glial cell basal endfeet mediate interneuron organization in the developing cortex

Authors: ***C.-F. LEE**[1], B. R. D'ARCY[2], C. M. MUSSO[2], L. J. PILAZ[2,6,7], D. L. SILVER[1,2,3,4,5]; [1]Dept. of Neurobio., [2]Dept. of Mol. Genet. and Microbiology, [3]Duke Regeneration Ctr., [4]Duke Inst. of Brain Sci., [5]Dept. of Cell Biol., Duke Univ., Durham, NC; [6]Dept. of Pediatrics, Sanford Sch. of Med., Univ. of South Dakota, Sioux Falls, SD; [7]Pediatrics and Rare Dis. Group, Sanford Res., Sioux Falls, SD

Abstract: Radial glial cells (RGCs) are neural progenitors that play an essential role in the development of the cerebral cortex. With a long basal process that extends towards the pial surface and apical and basal endfeet, RGCs' bipolar morphology serves as a scaffold to guide the radial migration of pyramidal neurons into different cortical layers. Yet, whether and how this distinct RGC morphology mediates the migration and positioning of interneurons in the developing cortex is largely unknown. Here, we focus on RGC basal endfeet, a subcellular compartment that resides in the marginal zone (MZ), one of the prominent routes taken by tangentially migrating interneurons. To uncover new roles for RGC basal endfeet in interneuron organization, we examine functions of proteins that we found are highly enriched in endfeet. We utilize siRNAs to knockdown the RhoGAP ARHGAP11A in mice and through live and fixed *ex vivo* and *in vivo* imaging, observe a significant decrease in RGC branching and basal process complexity. This disruption in morphology yields fewer interneurons touching the basement membrane within the MZ, while rescuing the morphology by localizing *Arhgap11a* to endfeet restores proper interneuron positioning. Genetic depletion of non-muscle myosin II heavy chain A (NM-IIA/MYH9) from RGCs largely phenocopies *Arhgap11a* mutants. Following dynein cytoplasmic 1 light intermediate chain 2 (*Dync1li2*) RGC knockdown, we observe an increase in RGC branching complexity and fewer interneurons within the MZ. In contrast, when endfeet are detached from the basement membrane in NM-IIB (MYH10) conditional knockout mice, we

observe a notable increase in the number of interneurons within the MZ. These findings demonstrate diverse roles for localized proteins in maintaining RGC integrity and non-cell autonomously mediating interneuron organization in the cerebral cortex. Our ongoing studies aim to interrogate the mechanism(s) underlying RGC-interneuron interactions, which can deepen our understanding of the cytoarchitecture of the cerebral cortex.

Disclosures: C. Lee: None. **B.R. D'Arcy:** None. **C.M. Musso:** None. **L.J. Pilaz:** None. **D.L. Silver:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

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Program #/Poster #: PSTR246.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: KIOM Grant KSN2022230
NRF Grant 2022R1C1C1006145

Title: Pro-neurogenic effects of Lilii Bulbus on hippocampal neurogenesis and memory

Authors: *H. PARK[1], W.-K. CHO[2], J. MA[2];
[1]KOREA INSTITUTE OF ORIENTAL MEDICINE, Daejeon, Korea, Republic of; [2]Korean Med. (KM)-Application Ctr., Korea Inst. of Oriental Med. (KIOM), Daegu, Korea, Republic of

Abstract: Lilii Bulbus, the bulb of tiger lily, has anti-oxidant and anti-tumorigenic properties. However, the effects of Lilii Bulbus on learning, memory, and hippocampal neurogenesis remain unknown. This study investigated whether water extract of Lilii Bulbus (WELB) affects memory ability and hippocampal neurogenesis. Behavioral analyses (Morris water maze and passive avoidance test), immunohistochemistry, cell proliferation assay, and immunoblot analysis were performed. WELB (50 and 100 mg/kg; for 14 days) enhanced memory retention and spatial memory in normal mice as well as in scopolamine-treated mice with memory deficits. Furthermore, the administration of WELB significantly increased the number of proliferating cells and surviving newborn cells in the dentate gyrus of the hippocampus in normal mice. We found that WELB has a pro-neurogenic effect by increasing the activation of brain-derived neurotrophic factor (BDNF)/cAMP response element-binding protein (CREB) and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK/ERK) in the hippocampus. Moreover, we confirmed that WELB (100 and 200 μg/ml) significantly increased NE-4C and primary embryonic NSCs proliferation. Inhibition/knockdown of MEK/ERK blocked WELB-induced MEK/ERK phosphorylation and NSCs proliferation. Hence, MEK/ERK activation was required in WELB-induced NSCs proliferation. Our study demonstrates the first evidence for WELB promoting hippocampal neurogenesis and memory; pro-neurogenic activity may enhance brain plasticity, with implications for treating neurodegenerative diseases.

Disclosures: H. Park: None. **W. Cho:** None. **J. Ma:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: Rare Diseases: Model and Mechanisms Grant 211108-001-001

Title: Investigating the role of the deubiquitinase USP15 in the development of the murine cerebral cortex

Authors: *K. BURNS, P. AU, G. YANG;
Univ. of Calgary, Calgary, AB, Canada

Abstract: The cerebral cortex is involved in processing higher-order tasks such as thinking, learning, and understanding sensory input. The development of the cortex is an intricate and highly regulated process that is susceptible to changes or disruptions to protein expression levels. One class of enzymes which contributes to the proteostasis of cells are deubiquitinases (DUBs), which typically remove ubiquitin from targets and save them from degradation. DUBs have not been well studied in the context of brain development, but some studies have found they can play important roles in the brain. Our objective is to explore whether the DUB, USP15, plays a role in cortical development. Using quantitative real-time PCR and immunohistochemistry, we assessed USP15 expression levels in the developing cerebral cortex of male and female mice from embryonic day 12 (E12) to postnatal day 21 (P21) (n=3). We found that USP15 is expressed in the cortex throughout development, peaking at P3 and then reducing into adulthood. To address USP15 function, we performed in utero electroporation of embryos at E13, and five days later, neurons with ectopic expression of USP15 showed a significant alteration in their distribution across the cortex compared to control neurons ($n = 7$, $\chi^2=54.4$, $p<0.0001$), suggesting that USP15 impacts how cortical neurons migrate during cortical development. Interestingly, USP15 subcellular localization appears to be different amongst cell populations, with neural precursor cells having more cytoplasmic USP15 than migrating post-mitotic neurons. Correspondingly, changes to USP15 nucleocytoplasmic localization altered neuronal migration in the developing cortex. In conclusion, our study reveals that the nucleocytoplasmic localization of USP15 in newborn neurons is critical for their proper migration during cortical development.

Disclosures: K. Burns: None. **P. Au:** None. **G. Yang:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Title: A BAIAP3 variant in males with pubertal failure: role of BAIAP3, a dense core vesicle protein, in the development and functioning of the hypothalamo-pituitary-gonadal axis

Authors: *M. AKRAM[1], S. WRAY[2];
[1]NINDS, NIH, Bethesda, MD; [2]NIH NINDS, NIH NINDS, Bethesda, MD

Abstract: Puberty is a crucial biological process leading to sexual maturation and reproduction. Puberty is controlled by the hypothalamo-pituitary-gonadal (HPG) axis, where secretion from gonadotropin releasing hormone (GnRH) neurons stimulates pituitary gonadotropes to release follicle stimulating hormone (FSH) and luteinizing hormone (LH), which subsequently activate the gonads. Any interruption in the development and/or regulation of the components of this axis may result in short-term or long-lasting dysfunction of reproductive axis such as delayed puberty and/or infertility. Delayed puberty in boys is defined as the deficiency of masculinization and increase in the volume of testes (testicular volume <4 mL) in combination with absent or low sperm count until 14 years of age. Notably, the genetic basis of delayed puberty in humans remains unknown in majority of the cases. Therefore, whole exome sequencing (WES) of genomic DNA was carried out on 6 male patients, over 18 years of age, exhibiting failed puberty. WES with bioinformatics analysis identified non-synonymous variants in 16 genes expressed along different pathways of the HPG axis which could cause failed male puberty. Out of 16 genes, 4 genes (*IL*17*RD*, *SPRY*4, *GNRHR*, *FLNA*) were previously reported to cause delayed puberty, 4 genes (*NPBWR*1, *SLC*17*A*6, *CACNA*1*B*, *CAPRIN*2) were expressed along the HPG axis but no mutations therein were reported to cause delayed puberty and 8 genes (*SRRM*4, *EFHC*1, *ERMARD*, *ATP*2*B*3,*BAIAP*3, *ADCY*8, *MAPK*6, *C*1*ORF*86) were novel candidate genes (Akram et al., 2022). To validate these novel genes, each one must be systematically examined along the HPG axis and subsequently perturbed in a model system. *BAIAP*3 (brain-specific angiogenesis inhibitor I-associated protein 3) was chosen due to its role in neuropeptide secretion and expression in cells in nasal areas during embryonic development, coinciding with the migratory route taken by GnRH neurons (Allen brain atlas). Microarray data showed expression of BAIAP3 increased as GnRH cells stopped migration. STRING analysis indicates connections of BAIAP3 protein with neuropeptides B (NPB) and W (NPW) and their receptor, NPBWR1. A mutation in *NPBWR*1 was also identified in this patient. Therefore, to determine the role of *BAIAP*3 gene in the HPG axis, expression of the protein will be examined in GnRH neurons as well as pituitary gonadotropes during pre- and postnatal development. Subsequently, *in vivo* and *in vitro* mouse models will be used to study the effect of WT and mutant/lack of *BAIAP*3 on the function of these important components of the HPG axis.

Disclosures: **M. Akram:** None. **S. Wray:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC 81871079

Title: Csde1 mediates neurogenesis via post-transcriptional regulation of cell cycle

Authors: *X. JIA, K. XIA, H. GUO;
Central South Univ., Changsha, China

Abstract: Autism spectrum disorder (ASD) represents a group of neurodevelopmental disorders with substantial genetic and clinical heterogeneity. We previously reported that disruptive variants in *CSDE1* increase ASD risk and interfere with neuronal development and synaptic transmission. However, whether and how CSDE1 regulates neurogenesis is still unknown. By analyzing a Csde1 conditional (Nestin-cre) knockout mouse model, we revealed that *Csde1* knockout results in defective neural progenitor proliferation and differentiation that manifests in number reduction of neurons in both deeper and upper layers. RNA-seq and CLIP-seq data implicated that Csde1 facilitate the transcription of multiple cell cycle genes including CDK6. RIP-qPCR further confirmed that CSDE1 regulate cell cycle genes by directly binding to the mRNA. By introducing BrdU incorporation experiment, we demonstrated that the cell cycles of neural progenitors were prolonged in *Csde1* knockout mice. Our findings demonstrated that *Csde1* mediates neurogenesis via post-transcriptional regulation of cell cycle network, which provide new insights into the neurodevelopmental roles of *Csde1*.

Disclosures: X. Jia: None. **K. Xia:** None. **H. Guo:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.08

Topic: A.01. Neurogenesis and Gliogenesis

Title: Visualization of secretory events in GnRH neurons

Authors: *F. SHAFIGHI, S. WRAY;
Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD

Abstract: The hypothalamic-pituitary-gonadal (HPG) axis controls reproduction. According to the World Health Organization, fertility disorders affect millions of individuals worldwide. Potential dysfunction(s) leading to infertility can occur at one or more levels of the HPG axis. Within the hypothalamus, Gonadotropin-releasing hormone (GnRH) secreting neurons play a critical role in integrating extrinsic and intrinsic cues that regulate puberty, fertility, and sexual behavior. This population of neurons secretes GnRH in a pulsatile manner into the portal capillary system, activating gonadotropes of the pituitary gland to release luteinizing hormone

(LH) and follicle-stimulation hormone (FSH) which act on the gonads to regulate the reproductive function. Dysfunction of the GnRH neurons can cause a physiological 'domino' effect that subsequently leads to delayed onset of puberty, infertility, and other reproductive disorders. The secretory behavior of GnRH neurons is not well understood. To clarify how GnRH is released in a pulsatile fashion, we need to understand the cellular and molecular mechanisms involved. Thus, to visualize GnRH secretion, we are using an explant model that maintains many of the characteristic of GnRH cells reported in postnatal mice, including pulsatile secretion. The paradigm includes loading GnRH dense core vesicles (DCVs) with Neuropeptide Y - GFP fluorescent cargo using an AAV9 viral vector containing the GnRH-NPY-hGFP sequence. Preliminary data indicate that the NPY-GFP DCV tag was incorporated into GnRH cells. High resolution microscopy is being used to verify that expression of the tag is restricted to DCVs using DCV markers such as chromogranin A and carboxypeptidase E. Subsequently, we will visualize GnRH DCVs travelling down the axons to their terminals in situ under basal and kisspeptin (a peptide known to cause GnRH release in vivo) stimulated conditions. Delineating the mechanisms involved in GnRH neuropeptide secretion will facilitate our understanding of the physiology of these neuroendocrine cells, as well as provide candidate genes to screen in patients with reproductive dysfunctions.

Disclosures: F. Shafighi: None. **S. Wray:** None.

Poster

PSTR246. Cell Proliferation and Migration II

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Program #/Poster #: PSTR246.09/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: NRF-2020R1C1C101024514
NRF-2021R1A6A3A0108712412
NRF-2022M3E5E801739512

Title: Anoctamin 1, a Ca^{2+}-activated Cl^- channel, regulates the proliferation of radial glia in the medial ganglionic eminence

Authors: *K. KIM[1], B. KANG[1], P. LEE[1], H.-Y. KIM[1], M.-S. KIM[1], U. OH[2], G.-S. HONG[1]; [1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Korea Inst. of Sci. and Technol. (KIST), Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

Abstract: Development of the central nervous system (CNS) requires the fine regulation of neurogenesis and gliogenesis by ventral radial glia (vRG). In a previous study, we exploited high resolution RNAscope experiment to investigate the spatio-temporal expression patterns of *Ano1* during the neurogenic period in embryonic brain. The majority of *Ano1* transcripts was were highly expressed in *Fabp7*+ and *Sox2*+ vRGs of the medial ganglionic eminence (MGE) from E11.5 to E14.5. In the present study, we checked examined whether ANO1 controls vRG fate in

MGE during early- to mid-neurogenic period. A decreased ratio of EdU-positive cells was observed in *Ano1*-ablated MGE at E14.5. Furthermore, the immunostaining experiments revealed a the decreased population of GABAergic neurons in the cortex of *Ano1* KO mice at E18.55 as a consequence. However, the ratio of intermediate progenitors (IP) was shown to be increased whereas the ratio of RG did not changed in MGE of *AnoNO1* KO mice. We therefore suggestpropose that *Ano1* promotes vRG proliferation. and may switch drive vRG fate to a basal rather than apical progenitors during GABAergic neurogenesis.

Disclosures: K. Kim: None. **B. Kang:** None. **P. Lee:** None. **H. Kim:** None. **M. Kim:** None. **U. Oh:** None. **G. Hong:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.10/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: Taiwan International Graduate Program

Title: Specific contribution of Dbx1 neuronal lineage to the Piriform Cortex

Authors: *T. W. SHABANGU[1,2,4], S.-J. CHOU[3], C.-F. F. CHEN[5], H.-L. CHEN[4], Z.-H. ZHUANG[3], A. PIERANI[6];
[1]Med. Physiol., Univ. of Stellenbosch, Bellville, Cape Town, South Africa; [2]Taiwan Intl. Grad. Program, Mol. Cell Biol., [3]Inst. of Cell. and Organismal Biol., Academia Sinica, Taipei, Taiwan; [4]Grad. Inst. of Life Sci., Natl. Def. Med. Ctr., Taipei, Taiwan; [5]Grad. Inst. of Life Sci., Natl. Def. Library, Taipei City, Taiwan; [6]Team Genet. and Develop. of the Cerebral Cortex, Imagine Inst., Paris, France

Abstract: The piriform cortex (PC) is a major cortical processing center for the sense of smell that receives direct inputs from the olfactory bulb. In mice, the PC consists of three neuronal layers, which are populated by cells with distinct developmental origins. One origin of PC neurons is the pool of Dbx1-expressing neural progenitors located in the ventral pallium at the pallial-subpallial boundary. Since the precise mechanisms of PC neuron development are largely unknown, we sought to define the distribution, timing of neurogenesis, morphology and projection patterns of PC neurons from the Dbx1 lineage. We found that Dbx1-lineage neurons are preferentially distributed in layer 2 and enriched in the ventral portion of the PC. Further, Dbx1 neurons are early-born neurons and contribute to most neuronal subtypes in the PC. Our data also revealed an enrichment of Dbx1-lineage neurons in the ventral anterior PC that project to the orbitofrontal cortex. These findings suggest a specific association between the developmental origin of PC neurons and their neuronal properties.
Thando Shabangu1,2,3, Hung-Lun Chen2, Zi-hui Zhuang3, Alessandra Pierani4,5, Chien-Fu F. Chen1,2* & Shen-Ju Chou1,2,3*

Disclosures: **T.W. Shabangu:** None. **S. Chou:** None. **C.F. Chen:** None. **H. Chen:** None. **Z. Zhuang:** None. **A. Pierani:** None.

Poster

PSTR246. Cell Proliferation and Migration II

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Program #/Poster #: PSTR246.11/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: Neuratris ACACIA

Title: Mct8 and dio2 regulate the transcriptional and cellular landscape of the adult mouse subventricular zone

Authors: *S. REMAUD[1], V. VALCÁRCEL-HERNÁNDEZ[2], P. VANCAMP[1], A. GUADAÑO[2];
[1]CNRS MNHN 7221, PARIS, France; [2]Inst. de Investigaciones Biomédicas Alberto Sols, Madrid, Spain

Abstract: Activated neural stem cells (NSCs) in the adult rodent subventricular zone (SVZ) generate new neuroblasts and oligodendrocyte precursor cells (OPCs). Increased intracellular levels of T_3 - the transcriptional active form of thyroid hormones (THs) - maintain NSC and progenitor renewal and promote NSC/progenitor commitment preferentially toward a neuronal fate. However, how regulators of the TH pathway regulate T_3 availability in SVZ cells and how this regulation affects neurogliogenic processes, is less understood. Here, we used adult *Mct8/Dio2* double knockout (*Mct8/Dio2* KO) mice to assess the role of the TH transporter monocarboxylate transporter 8 (MCT8) and deiodinase type 2 (DIO2). First, we characterized which cell types expressed *Mct8* and *Dio2* in the adult SVZ. Our single-cell RNAseq on dissected SVZs revealed that absence of both MCT8 and DIO2 dysregulated the SVZ cells' transcriptome and increased the proportion of neuroblasts. Immunohistochemistry confirmed increased neuron/oligodendroglial ratios in the adult SVZ. In addition, OPC differentiation into mature myelinating oligodendrocytes was impaired in the corpus callosum. *Ex vivo neurosphere assay* showed increased progenitor proliferation and hampered neuronal migration. Accordingly, migration of SVZ-generated neuroblasts is impaired along the rostro- medial stream in *Mct8/Dio2* KO, thus modifying the cellular architecture of the olfactory bulbs. The observed lowered neuronal integration in the olfactory networks was associated with compromising short-term olfactory memory and discrimination in *Mct8/Dio2* KO mice, showing that absence of both TH regulators functionally impaired SVZ-neurogenesis. In conclusion, MCT8 and DIO2 are pivotal in adult murine SVZ homeostasis and function. Further elucidating their precise function offers new targets to manipulate neurogliogenesis in several white matter diseases including multiple sclerosis and MCT8-deficiency.

Disclosures: **S. Remaud:** None. **V. Valcárcel-Hernández:** None. **P. Vancamp:** None. **A. Guadaño:** None.

Poster

PSTR246. Cell Proliferation and Migration II

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Program #/Poster #: PSTR246.12/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS Grant 5R01NS116054
NICHD Grant 5R01HD102492

Title: Neural stem cell division and ciliation in the embryonic cerebral cortex are disrupted by loss of abscission protein Cep55

Authors: *K. LETTIERI, K. MCNEELY, J. LITTLE, N. DWYER;
Cell Biol., Univ. of Virginia, Charlottesville, VA

Abstract: Proper proliferation of neural stem cells (NSCs) during development is essential for building an appropriately sized cerebral cortex. Defects to these processes can lead to lethal brain malformations such as microcephaly. Primary cilia play an important role regulating the cell cycle of these NSCs. Cilia are microtubule-based structures that protrude from the apical membrane of NSCs into the ventricle. They sense the extracellular environment and regulate signaling pathways. Moreover, primary cilia assembly and disassembly is coupled to the cell cycle. Before a cell can re-enter mitosis, the primary cilium needs to be disassembled to release the centrioles to form the mitotic spindle poles. After mitosis is complete, and during late cytokinesis (abscission), the primary cilia are reassembled. Cep55 is a scaffolding protein with an important role in cytokinetic abscission, required for efficient severing of the midbody in the intercellular bridge. It was also reported to localized to centrosomes. In humans, Cep55 mutations were shown to cause multiple brain malformations. Our previous analyses of *Cep55* knockout (KO) mouse brains showed that Cep55 localizes to the center of NSC midbodies, and promotes ESCRT-III recruitment and the timely disassembly of midbody microtubules. KO brains display many binucleate cells, but most NSCs can still complete abscission. In the brain, but not other tissues, cells that fail abscission activate p53-dependent apoptosis. This results in severe microcephaly, but preservation of normal body size (J. Nsci. 41(15):3344). To better understand how loss of Cep55 affects NSC proliferation, we asked whether primary cilia of NSCs were also affected. To address this, we assessed the primary cilia of embryonic cerebral cortex NSCs. Interestingly, cilia length and the number of biciliated NSCs were affected. In addition, we noticed enlarged apical endfeet (AE) of *Cep55* KO NSCs. To determine whether these enlarged AE were due to high levels of apoptosis, we blocked apoptosis by breeding *Cep55;p53* double KOs (dKO). However, blocking apoptosis did not rescue the large AE phenotype, but exacerbated it. Furthermore, the nuclei and cilia of these extra-large AE appear abnormal. Our data are consistent with Cep55 having an indirect effect on cilia due to its role in

abscission. Through this ongoing experimentation, we hope to gain further insight into how Cep55 function regulates proper NSC proliferation and brain growth.

Disclosures: K. Lettieri: None. **K. McNeely:** None. **J. Little:** None. **N. Dwyer:** None.

Poster

PSTR246. Cell Proliferation and Migration II

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.13/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: 2022M3E5E801739512
2020R1C1C101024514

Title: Expression patterns of Piezo1 in the developing mouse forebrain.

Authors: *H. KIM, P.-R. LEE, G.-S. HONG;
Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Malformation in cortical development disrupts excitatory/inhibitory neural circuits associated with psychiatric and developmental disorders. One of the key factors of cortical neural networks is fine regulation of neurogenesis. A variety of researches on embryonic development have documented important transcription factors and neurotrophic factors. However, there are still unanswered questions for the role of ion channels in embrogenesis and neurodevelopment. The recent emerging field of mechanobiology reveals that mechanical cues, such as cytoskeletal movements, shear stress and the forces exerted by neighboring cells, are regarded as important regulators for embryonic development. Piezo1, a mechanically-activated ion channel, is involved in NSC fate control and cell migration. However, its functional expression and the role during embryonic development *in vivo* remain unexplored. Therefore, to address this question, we conducted an RNAscope experiment to visualize the location of *Piezo1* with several embryonic neuronal/glial lineage cell markers. Furthermore, embryonic brain slice calcium imaging was performed to measure the functional expression of Piezo1. Our data demonstrates that Piezo1 mRNA is expressed in migrating interneurons and oligodendrocyte progenitor cells during the embryonic forebrain development.

Disclosures: H. Kim: 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.; 2020R1C1C101024514, 2022M3E5E801739512. **P. Lee:** None. **G. Hong:** 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.; 2020R1C1C101024514, 2022M3E5E801739512.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.14/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Institutes of Health [R01-NS117757 (D.K.C., J.C.O., E.M.P.)]
National Science Foundation [DGE-1845298 (E.M.P.)]
Department of Veterans Affairs [RR&D Career Development Award IK2-RX003376 (J.C.O.)]

Title: A tissue-engineered rostral migratory stream as an in vitro platform to investigate subventricular zone-derived neuroblast migration

Authors: *E. KRIZMAN[1,2], E. M. PURVIS[1,2,3], A. D. GARCIA-EPELBOIM[1,2], J. C. O'DONNELL[1,2], D. CULLEN[1,2,4];
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Abstract: Brain injury can result in progressive neuronal loss that is exacerbated by the limited regenerative capacity of the central nervous system. The rostral migratory stream (RMS) facilitates neuroblast migration from the subventricular zone to the olfactory bulb throughout adulthood. Brain lesions attract neuroblast migration out of the RMS, but resultant regeneration is insufficient without intervention. Our lab has biofabricated a “living scaffold” that is implanted to enhance endogenous neuroblast migration from the subventricular zone to neuron-deficient brain regions. This approach utilizes the first biomimetic tissue-engineered RMS (TE-RMS), designed to leverage the brain’s natural mechanism for sustained neuronal replacement by replicating the native RMS to direct neuroblasts to distal sites of injury. Our previous work has characterized the structure of the TE-RMS fabricated from both rat and human astrocyte cell sources. In addition to a promising new strategy for endogenous neuronal replacement, the TE-RMS is a powerful tool to unlock previously unanswered questions about adult neurogenesis. Here, we focus on the *in vitro* applications of the TE-RMS. We report an improved method of TE-RMS fabrication that has augmented construct survival and stability compared to previous methods. Specifically, we fabricated TE-RMSs using 4 different custom-designed micro-channel architectures featuring concave, convex, and orthogonal wall geometries (n=27 per group). Excitingly, TE-RMSs successfully self-assembled in all 4 channel geometries, demonstrating that the TE-RMS can form in the presence of various topographical conditions. Fabrication in a rectangular channel geometry had the highest success rate and therefore this channel shape was selected for subsequent *in vitro* studies. We also demonstrate that we can harvest neural precursor cells (NPCs) from the SVZ of adult male and female rats and culture them as neurospheres that reliably express stem cell markers. Following loading of SVZ-derived neurospheres into the end of TE-RMSs, individual neuroblasts migrated out of the neurospheres

and throughout TE-RMSs toward “destination” co-cultures consisting of rat cortical neurons and astrocytes. Our tissue engineered system allows for the examination of maturation and integration patterns of SVZ-derived neuroblasts following migration through the TE-RMS and into destination co-cultures *in vitro*. Overall, the TE-RMS provides a unique *in vitro* platform to examine SVZ neuroblast migration and maturation, providing an avenue to investigate key chemical and molecular cues in these complex processes.

Disclosures: **E. Krizman:** None. **E.M. Purvis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U.S. Provisional Patent App. 63/197,007 titled “Tissue-engineered rostral migratory stream for neuronal replacement”. **A.D. Garcia-Epelboim:** None. **J.C. O'Donnell:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); U.S. Provisional Patent App. 63/197,007 titled “Tissue-engineered rostral migratory stream for neuronal replacement”. **D. Cullen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); D.K.C. is a co-founder of two University of Pennsylvania spin-out companies concentrating in applications of neuroregenerative medicine: Innervace, Inc. and Axonova Medical, LLC; U.S. Patent App. 15/5.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.15/A14

Topic: A.01. Neurogenesis and Gliogenesis

Title: Regulation of Cerebral Cortex Folding by Controlling Neuronal Migration and Progenitor Expansion

Authors: *S. CHUN[1], S. DIAZ ALMEIDA[1], M. I. TODOROV[2,3,4], A. ERTÜRK[2,3,4], D. DEL TORO[5], S. SHI[6], R. KLEIN[1];
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Abstract: Cerebral cortex folding represents an important evolutionary mechanism that is incompletely understood. Present evidence suggests that cortex folding is caused by two cellular mechanisms: (1) expansion of progenitor cells and (2) divergent radial migration of neurons. We have previously generated a mouse model (*Flrt1/Flrt3* DKO; del Toro et al., 2017) with sulci-like folding induced by divergent radial neuronal migration without expansion of progenitor cells. We have used this ‘cell migration’ model to ask if the two folding mechanisms synergize

and whether the expansion of certain types of progenitors leads to qualitatively different cortical folds. We report that increasing the length of the early cortical stem cell expansion phase by deletion of fibroblast growth factor 10 (FGF10) in the 'cell migration' model (*Fgf10/Flrt1/Flrt3*^{TKO}, we now call *Fgf10*^{TKO}) leads to cortical folding with increased penetrance and, importantly, with gyrus-like protrusions. Conversely, overproduction of intermediate progenitors by deletion of centrosomal protein 83 (Cep83) in the 'cell migration' model (*Cep83/Flrt1/Flrt3*^{TKO}, we now call *Cep83*^{TKO}) leads to cortical folding with increased penetrance and sulci-like appearance. These results indicate that expansion of progenitor cells and divergent radial migration of neurons synergize in vivo to induce cortical folding. They further show that expanding different types of progenitors can lead to qualitatively different folding, suggesting that the formation of gyri and sulci requires the timely expansion of distinct progenitors.

Disclosures: S. Chun: None. **S. Diaz Almeida:** None. **M.I. Todorov:** None. **A. Ertürk:** None. **D. Del Toro:** None. **S. Shi:** None. **R. Klein:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.16/A15

Topic: A.01. Neurogenesis and Gliogenesis

Support: Grant from Office of Principal Scientific Adviser, the Government of India
Grant from the Pratiksha Trust, India
Other support for PPM from H N Mahabala Chair Professorship of the Indian Institute of Technology Madras

Title: Insights into the early development of primary sulci in the developing human brain using a high-resolution multimodal histological pipeline

Authors: R. VERMA[1], *J. JAYAKUMAR[4], S. KARTHIK[2], R. KUMARASAMI[2], S. SAVOIA[5], P. P. MITRA[5], J. JOSEPH[3], M. SIVAPRAKASAM[3];
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Abstract: Cellular-level histological data still remains the gold standard for studying the organization of developing human brains. Obtaining histological data from the whole fetal brain is currently sparse, primarily due to the challenges including the retrieval and acquisition of high-quality postmortem specimens and the difficulties in the subsequent processing of these brains due to its high-water content. Employing a technology-enabled high-resolution multimodal imaging pipeline consisting of postmortem MRI, blockface imaging, and high-

resolution histology, we characterize the developmental patterns of the fetal brain from 13 to 21 Gestational Weeks (GW) (n=5). The whole brain specimens were sectioned in the sagittal plane at 20µm thickness and stained for three series Nissl, Hematoxylin and Eosin and Immunohistochemistry (IHC). Our histological data, 13-15 GW, shows the appearance of early-stage sulcal roots, particularly on the mesial surface. We report the well-organized laminar organization of the sulcal roots, showing the transient developing layers from the ventricular zone to the marginal zone. We also describe the developing pattern of the radial glial processes with Glial Fibrillary Acidic Protein (GFAP) IHC, which shows a similar pattern of labeling, to other regions in the cerebral cortex, that do not have these sulcal roots. We show the progression of these early sulcal roots into the cingulate sulcus from 13-21GW, mainly due to the changing size of the lateral ventricles, and the increase in neuropil. Our results show a systematic progression of the developing brain and the primary sulci from 13-21 GW. The cellular-level dataset provides valuable comparative data for studying developmental delays and malformation in the developing human brain.

Disclosures: **R. Verma:** None. **J. Jayakumar:** None. **S. Karthik:** None. **R. Kumarasami:** None. **S. Savoia:** None. **P.P. Mitra:** None. **J. Joseph:** None. **M. Sivaprakasam:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.17/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860035

Title: Analysis of the role of YIPF5 in ER-export and Microcephaly

Authors: ***F. BRUNO**[1], M. ANITEI[1], D. DI FRAIA[1], M. SANNAI[1], I. MESTRES[2], T. DAU[1], A. ORI[1], F. CALEGARI[2], C. KAETHER[1];
[1]Leibniz Inst. on Aging - Fritz Lipmann Inst. (FLI), Jena, Germany; [2]Ctr. for Regenerative Therapies Dresden (CRTD), Dresden, Germany

Abstract: YIPF5 and SURF4 proteins are crucial for transporting the endoplasmic reticulum and the Golgi. YIPF5 mutations have been associated with primary microcephaly and neonatal diabetes. This study investigates the impact of YIPF5 depletion or mutation on cellular migration in vitro and in vivo. We utilized the IncuCyte system and a wound healing assay to observe wound density changes over a 15-hour live imaging acquisition period (n=3). We found that YIPF5 absence or mutation significantly affected cellular migration. Additionally, we conducted a proteomic analysis of Immunoprecipitated-YIPF5 to identify its interaction partners, and discovered that SURF4 strongly interacts with YIPF5, the finding was validated via WB and Immunofluorescence (IF).To investigate the influence of YIPF5 on neuronal migration, GFP-

tagged shLuciferase and shYIPF5 constructs were electroporated into E13 mouse embryos. EdU was injected at E14.5 to label dividing cells, and GFP-expressing neurons were visualized by immunostaining at E15.5. Cortical sections were treated with the EdU staining kit, and the distribution of GFP-positive neurons was examined via IF in the cortical plate (CP), three sections of the intermediate zone, and the Ventricular zone-Subventricular Zone. (n=6). Quantification of the percentage distribution of GFP-positive-shYIPF5 neurons in each cortical layer was compared to the shLuciferase control group. Intriguingly, the analysis revealed a significant increase in the number of YIPF5-knockdown neurons in the cortical plate (CP). This observation suggests an over-migration phenotype, indicating that YIPF5 depletion leads to abnormal migration of neurons into the CP. Secretome and cell-surface proteomics analyses reveal that YIPF5 regulates the ER exit of specific proteins essential for neurodevelopment, cell migration, and cell adhesion. The insufficient presence of these proteins at the plasma membrane due to YIPF5 depletion or mutation may contribute to dysregulated neuronal migration and associated phenotypes, such as microcephaly. The proteomic findings, combined with the in-utero electroporation experiments, highlight the crucial role of YIPF5 in regulating proper neuronal migration during cortical development. Our results provide compelling evidence of the YIPF5-SURF4 interaction and YIPF5´s involvement in neuronal migration. This study contributes to the understanding of the molecular mechanisms underlying proper cortical layer formation and emphasizes the potential implications of disrupted YIPF5-SURF4 interactions in neurodevelopmental disorders associated with aberrant neuronal migration, such as microcephaly.

Disclosures: **F. Bruno:** None. **M. Anitei:** None. **D. Di Fraia:** None. **M. Sannai:** None. **I. Mestres:** None. **T. Dau:** None. **A. Ori:** None. **F. Calegari:** None. **C. Kaether:** None.

Poster

PSTR246. Cell Proliferation and Migration II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR246.18/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: Eagles Autism Foundation
CT IBACS

Title: Transcriptional and behavioral abnormalities in mouse model of autism spectrum disorder with macrocephaly

Authors: S. SINGH[1], H. FARADAY[1], T. SPELLMAN[1], P. ROBSON[2], R. FITCH[3], ***B.-I. BAE**[1];
[1]Univ. of Connecticut Sch. of Med., Farmington, CT; [2]The Jackson Lab. for Genomic Med., Farmington, CT; [3]Psychological Sci., Univ. of Connecticut, Storrs Mansfield, CT

Abstract: Autism spectrum disorder (ASD) is a highly heritable, heterogeneous neurodevelopmental disorder affecting 1 in 36 children in the US, with a male-to-female prevalence ratio of 4:1. The cerebral cortex, particularly the prefrontal cortex, which mediates social cognition and language, is abnormally enlarged in up to 20% of young patients with ASD who have the most severe symptoms, but normalizes by early adulthood. However, it is unclear to what extent macrocephaly or megalencephaly itself contributes to ASD. Recently, we have developed a unique mouse model of ASD with macrocephaly and social deficits by knocking in an ASD-associated point mutation in the abnormal spindle-like microcephaly-associated (ASPM) gene, a major determinant of brain size, particularly in the prefrontal cortex. Aspm knock-in (KI) mice show excessive embryonic neurogenesis with increased progenitor proliferation and cortical thickness resulting in macrocephaly between embryonic day 14.5 (E14.5) and postnatal day 10 (P10). Interestingly, macrocephaly normalizes around P50, similar to the time course of macrocephaly in human patients with ASD. Aspm KI mice also exhibit reduced density of inhibitory synapses at P10, which normalizes at P50. Importantly, male KI mice show deficits in the social novelty test, whereas female KI mice do not, suggesting sex-specific effects. We are currently investigating transcriptional abnormalities at the single cell level and behavioral abnormalities (e.g. ultrasonic vocalizations, cognitive flexibility) in KI mice. In summary, we are rigorously testing the hypothesis that excessive embryonic neurogenesis is sufficient to induce at least some ASD-like behaviors in male mice by disrupting transcription, cell composition, and synaptic connectivity.

Disclosures: S. Singh: None. **H. Faraday:** None. **T. Spellman:** None. **P. Robson:** None. **R. Fitch:** None. **B. Bae:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.01/A18

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant R00 EY027467-05

Title: Tracking the zebrafish optic nerve regeneration using the optokinetic response

Authors: S. YOUNG, M. HORUTZ, A. TIEMAN, A. HERMANS, S. TAJNAI, ***S. J. HENLE**; Neurosci., Carthage Col., Kenosha, WI

Abstract: Zebrafish have eyes similar to humans making them a useful model organism for studying vision. However, zebrafish are different in that they are able to regenerate their optic nerve after injury. Measuring vision in people who have communicative ability is achieved using eye charts. Fish cannot use an eye chart, so we utilize the optokinetic response (OKR) that is present in virtually all vertebrates to determine if a zebrafish has eyesight. The OKR is observed by monitoring eye movement in response to moving visual stimuli. By injuring the optic nerve

on a zebrafish we can track its regeneration by measuring the return of its OKR. Recorded videos of the OKR are then analyzed manually or by using DeepLabCut. Using the optokinetic response provides insight into the functional process of regeneration, whereas previous work has focused on the anatomical process. Additionally, it allows us to access regeneration in individual animals over time, unlike histological methods that require sacrificing the animal for a single timepoint. Moreover, we have designed an entire setup to measure the OKR in adult and larval zebrafish that is 3D printed and relies on open-source software. This will allow us to scale up more easily and potentially use this in classroom labs as well. Understanding the functional regeneration in zebrafish will aid in developing treatment for humans with optic nerve injuries.

Disclosures: S. Young: None. **M. Horutz:** None. **A. Tieman:** None. **A. Hermans:** None. **S. Tajnai:** None. **S.J. Henle:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.02/A19

Topic: A.04. Transplantation and Regeneration

Support: NIH R01-NS0117821
Adelson Medical Research Foundation
Craig H Neilsen Foundation (733151)
South Carolina Honors College SURF award

Title: Role of axonal G3BP1 granules in regeneration-challenging situations

Authors: *E. G. MASON[1], T. SMITH[1], S. MILLER[1], S. WARIYAR[2], P. WARD[2], A. W. ENGLISH[2], N. HANOVICE[3], J. N. DULIN[4], L. BENOWITZ[3], J. D. HOULE[5], P. K. SAHOO[1,6], J. L. TWISS[1];
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Abstract: Axonal mRNAs are translated into new proteins after neurotrauma and these new proteins are needed for regeneration. We previously showed that the stress granule protein G3BP1 serves as a mRNA storage depot in axons and slows axon growth after injury. Exogenously expressing the acidic domain of G3BP1 disassembles axonal G3BP1 granules and accelerates PNS axon growth. A cell-permeable peptide (CPP) consisting of G3BP1 amino acids 190-208 triggers rapid disassembly of axonal G3BP1 granules and promotes axon growth in culture. Here, we show that the 190-208 CPP increases axon regeneration and acutely improves NMJ reinnervation when applied 2 d after nerve crush. G3BP1 granules are also seen in CNS axons, including in the spinal cord. Following spinal cord transection, injured reticulospinal

axons will grow into the permissive environment of a peripheral nerve graft (PNG) but halt growth upon reaching the distal cord. AAV transduction of reticulospinal neurons with the G3BP1 acidic domain accelerates growth within the PNG. Similarly, AAV transduction of retinal ganglion cells with G3BP1 acidic domain increased axon regeneration following optic nerve crush, indicating that G3BP1 granules attenuate CNS axon regeneration. Surprisingly, injecting the 190-208 CPP into the proximal transected spinal cord triggered sprouting-type growth within a PNG. In contrast, injecting 190-208 CPP directly into the graft promoted axon growth across the distal interface back into the spinal cord. Finally, returning to the PNS, treatment with the 190-208 CPP did not increase regeneration in chronically injured sciatic nerve axons. Together with the sprouting response in reticulospinal neurons, this raises the interesting possibility that response to the 190-208 CPP, which triggers G3BP1 granule disassembly in acutely injured axons, is context-dependent and possibly influenced by the environment of the injured axon.

Disclosures: **E.G. Mason:** None. **T. Smith:** None. **S. Miller:** None. **S. Wariyar:** None. **P. Ward:** None. **A.W. English:** None. **N. Hanovice:** None. **J.N. Dulin:** None. **L. Benowitz:** None. **J.D. Houle:** None. **P.K. Sahoo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); JLT and PBS hold US patent on use of G3BP1 peptide for regeneration. **J.L. Twiss:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); JLT and PBS hold US patent on use of G3BP1 peptide for regeneration.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.03/A20

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant EY031403
NIH Grant EY029903
NIH Grant EY026877
Knights Templar Eye Foundation
Stanford MCHRI
Research to Prevent Blindness
Gilbert Vision Restoration Initiative

Title: Re-expression of developmental transcription factors induces generation of retinal-ganglion-cell-like neurons

Authors: *M. WOODWORTH[1], L. C. GREIG[2], B. K. YOUNG[3], E. L. HUIE[3], M. NAHMOU[3], J. L. GOLDBERG[3];

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Abstract: Retinal ganglion cells (RGCs) are a critically important retinal neuron type connecting the retina with the brain, and because the adult mammalian retina has minimal to no regenerative capability, irreversible visual impairment results from RGC injury or death. In this study, we aimed to identify a method to induce RGC development from endogenous retinal progenitor cells. *In vivo* postnatal electroporation of a set of candidate developmentally-expressed transcription factors induces development of RGC-like cells outside the window of endogenous RGC development. These induced RGCs represent a population distinct from endogenous RGCs. When forced to express this set of developmental transcription factors, retinal progenitors to first produce induced RGCs, then sequentially produce later retinal neuron types, uncoupling real time from developmental time. Induced RGCs express programs of genes characteristic of RGCs, and not of late-born retinal neurons or progenitors. Axons of induced RGCs progressively extend from the optic nerve, reaching visual targets in the thalamus and midbrain, but these projections are not maintained. Overall, we aim to understand the generation and development of new RGCs from existing cells intrinsic to the retina, which could enable restoration of vision in blind patients.

Disclosures: M. Woodworth: None. **L.C. Greig:** None. **B.K. Young:** None. **E.L. Huie:** None. **M. Nahmou:** None. **J.L. Goldberg:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.04/A21

Topic: A.04. Transplantation and Regeneration

Support: JSPS KAKENHI Grants-in-Aid for Scientific Research 20H03342
Nagahisa Science Foundation

Title: Bdnf promotes expression of lotus, an endogenous nogo receptor antagonist

Authors: *J. MATSUBAYASHI, Y. KAWAGUCHI, Y. KAWAKAMI, K. TAKEI; Neural Regenerative Med. Laboratory, Dept. of Regenerative Med., Yokohama City Univ. Sch. of Med., Yokohama, Japan

Abstract: Trauma and neurological disorders strongly limit neuronal regenerative capacity and give rise to irreversible loss of function in the adult mammalian CNS. The molecular interaction between axonal growth inhibitors (AGIs) derived from myelin debris and glial cells such as Nogo protein and its receptor, Nogo receptor-1 (NgR1) is major obstacle preventing neuronal repair in injured CNS. Therefore, blockade of the molecular interaction between AGIs and NgR1 is beneficial therapeutic target for CNS regeneration. Lateral olfactory tract usher substance (LOTUS) contributes to axonal tract formation in the developing brain and axon regrowth in the

injured adult brain as an endogenous NgR1 antagonist. Additionally, LOTUS enhances synapse formation and memory. Thus, LOTUS functions as a potent neuronal agent by inhibiting NgR1 functions. However, the expression level of LOTUS is drastically decreased after CNS injury and declines along with aging. Therefore, suppression of down-regulating LOTUS expression and supplementation of LOTUS can be effective to maintain “healthy” CNS environment, but how LOTUS expression is regulated remains elucidated. Herein, we examined molecular mechanism of regulation in LOTUS expression and found that brain-derived neurotrophic factor (BDNF) increases the expression level of LOTUS in cultured hippocampal neurons. Exogenous application of recombinant BDNF increased LOTUS expression approximately 50% at both mRNA and protein levels in cultured hippocampal neurons on days in vitro 7 (DIV 7). Pharmacological inhibition with K252a, a tropomyosin-related kinase B (TrkB) inhibitor, blockade of TrkB with decoy protein and gene knockdown of TrkB siRNA suppressed BDNF-induced increase in LOTUS expression. Further pharmacological analysis of the TrkB signaling pathways revealed that BDNF increases in LOTUS expression through mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) cascades. Furthermore, treatment with c-AMP response element binding protein (CREB) inhibitor partially suppressed BDNF-induced LOTUS expression. Finally, neurite outgrowth assay in cultured hippocampal neurons from wild-type mice and *lotus*-deficient mice revealed that BDNF-induced up-regulation of LOTUS promotes neurite outgrowth by antagonism for NgR1. Our findings suggest that BDNF may act as a positive regulator of LOTUS through TrkB receptor. We propose that increase of LOTUS expression by BDNF may be a beneficial therapeutic strategy for CNS injury as it is expected to be synergistic with axon growth-promoting effects of BDNF.

Disclosures: **J. Matsubayashi:** None. **Y. Kawaguchi:** None. **Y. Kawakami:** None. **K. Takei:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.05/A22

Topic: A.04. Transplantation and Regeneration

Support: 2021R1A2C2006110,

Title: Mechanical environment afforded by hydrogel determines the engraftment of the neural stem cells via regulation of cellular adhesion and survival in the injured spinal cord

Authors: *B. KIM[1], H. PARK[2];
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Abstract: The therapeutic potential of cell transplantation for spinal cord injury (SCI) is frequently compromised by poor survival of grafted cells. Biomaterial-based scaffolds may

support cellular engraftment in the inhospitable microenvironment of the injured spinal cord. We have previously demonstrated that injection of a thermosensitive injectable hydrogel can bridge cystic cavities accompanied by the formation of extracellular matrix (ECM) in the lesion epicenter that would otherwise become tissue defects following SCI. We initially expected that hydrogel-induced bridging effects would be highly conducive to graft survival. However, E14 spinal cord-derived neural stem cells (NSCs) delivered as a complex with the hydrogel barely survived the transplantation with frequent graft failures. We hypothesized that the mechanical properties of the hydrogel may be crucial to regulate the survival of NSCs transplanted within the hydrogel complex. Transplantation of NSCs with a varying percentage of hydrogel in the injured spinal cord showed a concentration-dependent increase in the areas of NSC grafts and engraftment rate *in vivo*, demonstrating that modulation of hydrogel mechanical stiffness can improve the survival of transplanted NSCs. To elucidate the molecular mechanisms underlying stiffness-dependent increase in graft survival, we established an *in vitro* culture system where NSCs were grown on hydrogel substrates with different stiffness ranging from 0.2 to 25 kPa. NSCs cultured on a rigid substrate showed an increase in the spreading area and cellular perimeter in a stiffness-dependent manner, indicating an improvement in cellular adhesion. This was accompanied by a significant increase and decrease in the percentage of living and dying cells, respectively. Moreover, NSCs cultured in a softer environment exhibited a compromise in cellular membrane elasticity and intracellular calcium oscillation, all of which were dependent on actin polymerization. We almost demonstrated that mechanical forces derived from substrate rigidity may be converted into biochemical events via mechanosensitive channels in the plasma membrane. Future studies will be carried out to determine whether mechanosensitive channels in NSCs with stiffer hydrogel are necessary for successful engraftment in the injured spinal cord.

Disclosures: B. Kim: None. **H. Park:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.06/A23

Topic: A.04. Transplantation and Regeneration

Title: Generation and characterization of exogenic microglia-like cells using blastocyst complementation

Authors: *P. STRELL[1], S. JOHNSON[2], A. SHETTY[3], W. C. LOW[4];
[1]Vet. and Biomed. Sci., Univ. of Minnesota, Saint Paul, MN; [2]Stem Cell Inst., [3]Molecular, Cellular, Developmental Biology, and Genet., [4]Neurosurg., Univ. of Minnesota, Minneapolis, MN

Abstract: Alzheimer’s disease (AD) is a degenerative brain disease that leads dementia diagnoses and impacts 6.2 million Americans 65 and older. Current treatments are limited, and neither stop the pathology of progressive beta-amyloid and tau accumulation, nor the neuronal

damage and loss. Microglia dysfunction has been implicated as a major contributing factor of AD, worsening neuronal loss and tau pathology. Yet healthy microglia show neuroprotective functions like regeneration, inflammatory response suppression, and reversal of behavioral deficits. Our aim is to develop a novel approach for a renewable source of young microglia. We hypothesize that targeting microglial genes for deletion in the embryo will create a niche to generate exogenic microglia-like cells, and these cells, in turn, recapitulate primary healthy microglia. Blastocyst complementation (BC) with pluripotent stem cells (PSCs) and targeted gene-edited embryos will be used to generate exogenic microglia-like cells.
Because the HHEX gene is involved in liver, forebrain, and hematopoietic system development, it is an early microglia development target gene, as microglia are derived from an early wave of hematopoiesis. *PU.1* is important in hematopoietic and myeloid cell development. *PU.1* deficient mice lack circulating monocytes, tissue macrophages, and parenchymal microglia in the brain. We engineered the loss of *HHEX* and *PU.1* gene expression in early mouse embryos and performed intraspecies BC of *HHEX* and *PU.1* KO embryos with eGFP-labeled PSCs to rescue microglia development.
In blastocysts, loss of *HHEX* gene results in a homozygous KO and heterozygous rate of 25.6% and 26.8%, respectively. Intraspecies BC of *HHEX* KO embryos led to the formation of microglia-like cells derived from both the eGFP-labeled donor-derived cells and host. We also observed a proportion of perivascular macrophages generated from the eGFP-labeled donor-derived cells. Loss of *PU.1* gene resulted in a homozygous and heterozygous KO rate of 28.6% in *PU.1*, and a homozygous KO rate of 66.7% and heterozygous KO rate of 16.7%, using two different constructs respectively. These results demonstrate that young microglia-like cells and perivascular macrophages can be generated via BC methods. However, the generation of the perivascular macrophages shows that *HHEX* may not be specific enough to only produce microglia, therefore *PU.1* may be a more specific gene target.

Disclosures: **P. Strell:** None. **S. Johnson:** None. **A. Shetty:** None. **W.C. Low:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.07/B1

Topic: A.04. Transplantation and Regeneration

Support: CONACYT Grant No. 181779
FODECIJAL Grant No. 8148

Title: Glial fibrillary acidic protein (GFAP) isoforms expression in bone marrow mesenchymal stem cells differentiated towards Schwann-like phenotype

Authors: *G. REYES-GUTIERREZ, N. CARRILLO-GONZÁLEZ, T. CAMPOS-ORDOÑEZ, G. ESCOBAR-CAMBEROS, Y. GASCA-MARTÍNEZ, G. GUDIÑO-CABRERA; Deparment of Mol. and Cell Biology-CUCBA, Univ. de Guadalajara, Zapopan, Mexico

Abstract: Central nervous system (CNS) has a limited capacity to repair and restore itself from the damage, however, CNS can contain it through reactive gliosis. Several strategies have been proposed to promote regeneration using cell therapy. Olfactory ensheathing cells (OECs) or Schwann-like cells can promote CNS reparation, but it is difficult their obtention and purification for cell therapy. Thus, we use a model based on bone marrow-mesenchymal stem cells (BM-MSC) differentiated into a phenotype Schwann-like cells (BM-MSCdif). Schwann cells express the glial fibrillary acidic protein mRNA isoforms β (GFAPβ), and GFAPδ isoform is characteristic of precursor cells. Therefore, we characterized the mRNA isoforms of GFAPβ and GFAPδ between three conditions: 1) primary cultures of OEC and 2) BM-MSC of adult Wistar rats; and 3) MSC cells exposed to olfactory ensheathing cells-conditioned medium (BM-MSCdif) to determine their possible use as a cell therapy. In our results, as we expected OEC with spindle-like morphology expressed CD73, p75 and GFAP; BM-MSC with fibroblast-like morphology showed CD90, CD73, p75, and GFAP; and BM-MSCdif showed spindle-like morphology and expressed CD73, p75 and GFAP by immunocytochemistry. In addition, all three cell types expressed GFAPβ and GFAPδ isoforms by end point PCR and RT-qPCR. Finally, we observed the diffuse granulated distribution of GFAP in the three cell types studied by immunocytochemistry. These data suggest that exist a possible morphological and molecular relationship in BM-MSCdif with OECs. Findings about GFAP and its isoforms are expressed in BM-MSC reveal the possibility to study the role of this cytoskeletal protein in neural regeneration processes.

Disclosures: G. Reyes-Gutierrez: None. **N. Carrillo-González:** None. **T. Campos-Ordoñez:** None. **G. Escobar-Camberos:** None. **Y. Gasca-Martínez:** None. **G. Gudiño-Cabrera:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.08/B2

Topic: A.04. Transplantation and Regeneration

Support: EY029739

Title: A recombinant protein derived from a component of the extra-axonal environment promotes retinal ganglion cell survival and axon regeneration after injury in vivo

Authors: *M. P. FROST, A. LUKOMSKA, B. A. RHEAUME, W. C. THEUNE, J. XING, E. F. TRAKHTENBERG;
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Abstract: Central nervous system (CNS) projection neurons in mammals fail to regenerate damaged axons and restore connections with appropriate targets following injury. Consequently, disruption of these axons by either stroke or traumatic injury results in irreversible loss of function and subsequent neuronal cell death. For example, retinal ganglion cells (RGCs) are the

major CNS projection neurons of the eye and are responsible for the relay of visual information to the brain through the optic nerve. Stroke or traumatic injury of RGC axons in the optic nerve results in blindness and progressive RGC cell death. Modest regeneration of CNS axons has been achieved by manipulation of neuronal intrinsic and extrinsic factors. However, currently there are no therapeutics available that can repair the CNS circuits damaged by such injuries. The failure of CNS neurons to regenerate their long-distance axons remains an important unmet clinical problem. Here, using bioinformatic analysis of single cell RNA-seq-profiled RGCs, we predicted extra-axonal environment molecules that could interact with the axons and regulate their growth. We then tested the effects of these molecules on adult RGCs, which otherwise survive poorly and do not grow long axons in culture. We found that one of these molecules (identity masked due to proprietary information) enabled a subset of axotomized adult RGCs to survive for a long period and stimulated long-distance axon growth in a permissive culture environment. Next, we synthesized a recombinant variant of this molecule, and found that its targeted delivery promoted axon regeneration after optic nerve crush injury *in vivo*. Thus, this recombinant molecule presents a novel potential therapeutic for neuroprotection and axon regeneration treatments.

Disclosures: **M.P. Frost:** None. **A. Lukomska:** None. **B.A. Rheaume:** None. **W.C. Theune:** None. **J. Xing:** None. **E.F. Trakhtenberg:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.09/B3

Topic: A.04. Transplantation and Regeneration

Support: NIH R01-EY029739

Title: Micrornas associated with maturation of retinal ganglion cells regulate survival and long-distance axon regeneration after optic nerve injury

Authors: *A. LUKOMSKA, W. THEUNE, J. XING, M. FROST, M. GUPTA, E. F. TRAKHTENBERG;
UCONN Sch. of Med., Farmington, CT

Abstract: Retinal ganglion cells (RGCs) are central nervous system (CNS) projection neurons, which do not regenerate axons severed in optic neuropathies, such as those resulting from optic nerve trauma, ischemia, and glaucoma. Several factors that are developmentally regulated in RGCs were discovered to contribute to their failure to regenerate the injured axons. No clinical treatments exist to date that could help patients with such axonal injuries. Thus, the failure of RGC and other CNS long-distance axons to regenerate after injury remains a major unmet problem. Here, we bioinformatically analyzed small-RNA-seq datasets, which we generated using RGCs purified from different stages of development, in order to identify developmentally-

regulated microRNAs (miRNAs). Then, we investigated the roles of the identified miRNAs in RGC survival and axon regeneration after optic nerve injury, using a well-established mouse *in vivo* model of optic nerve crush (ONC). The RGCs were pre-treated with intravitreally injected AAV2 vectors, which either upregulate or knockdown the candidate miRNAs. Two weeks later, ONC was performed and RGC survival and axon regeneration were evaluated two weeks after injury. We found several novel miRNA targets, which either promoted or inhibited RGC survival and axon regeneration. We then proceeded to test the identified novel miRNA-regulators of RGC survival and axon regeneration in a long-term assay, in which the extent of neuroprotection and axon regeneration was evaluated at 6 weeks after ONC injury. By this time-point after ONC, most RGCs usually die. However, for a few of the tested miRNA targets we found many-fold increase in RGC survival, and also detected axons that regenerated through the optic nerve, optic chiasm, and entered the optic tract. Thus, the identified novel miRNA-regulators of RGC survival and axon regeneration present potential therapeutic targets for treating optic neuropathies and glaucoma, as well as axonal injuries in other white matter tracts of the CNS.

Disclosures: **A. Lukomska:** None. **W. Theune:** None. **J. Xing:** None. **M. Frost:** None. **M. Gupta:** None. **E.F. Trakhtenberg:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.10/B4

Topic: A.04. Transplantation and Regeneration

Support: NIH R01 EY030458
Mallinckrodt Scholar Award
NIH Grant R01 EY024984
NIH Grant R01 EY033022
BrightFocus Foundation G2020369

Title: Reconstructing visual circuits to investigate synapse re-connection in hiPSC-retinal ganglion cells

Authors: *K.-C. HUANG[1], A. HO[2], C. GOMES[4], J. MEYER[4], M. A. SAMUEL[3]; [1]Huffington Ctr. on Aging, Baylor Col. of Med., Houston, TX; [2]Dept. of Neuroscience, Huffington Ctr. on Aging, Baylor Col. of Med., HOUSTON, TX; [3]Dept. of Neuroscience, Huffington Ctr. on Aging, Baylor Col. of Med., Houston, TX; [4]Indiana Univ. Sch. of Med., INDIANAPOLIS, IN

Abstract: Transplantation of donor neurons has emerged as an advantageous approach to repopulate neuron circuitry in the context of neuronal disorders. Yet, how to guide neurons to re-innervate appropriate brain targets is not clear. This is particularly challenging in the context of neurodegenerative diseases in the visual system because of the long-distance that axons from

retinal ganglion cells (RGCs) must traverse to reinnervate retinorecipient areas in the brain. To provide insight into cues that may guide RGC axon re-innervation, we aim to elucidate axonal pathfinding and synaptic connectivity pathways by reconstructing visual circuits in human induced-pluripotent stem cells (hiPSCs)-derived RGCs (hiPSC-RGCs). We first asked whether cultured hiPSC-RGCs can segregate their dendritic and axonal compartment in a partitioned microfluidic device connected by microgrooves. We found hiPSC-RGCs neurites successfully segregated into dendrites and axons, with marginal overlap between the dendritic and axonal markers MAP2 and SMI-312. Over the course of maturation, hiPSC-RGCs axons grew and crossed into the axonal chamber and exclusively expressed SMI-312. These data suggest that hiPSC-RGCs are able to polarize their dendrite and axon compartments properly. To study postsynaptic neuronal connectivity in the brain, we then co-cultured hiPSC-RGCs with mouse primary lateral geniculate nucleus (LGN) and suprachiasmatic nucleus (SCN) neurons, two major retinorecipient regions. We are currently examining whether co-culture improves neurite maturation by quantifying synapse density in hiPSC-RGCs neurites. Finally, we are extending our study to reconstruct visual circuits in a multi chamber microfluidic device to determine whether RGC axons connect specificity with LGN or SCN neurons. Together, our data suggest that an in vitro model of primary visual system connectivity can be used to inform synaptic specificity pathways. Such results will facilitate the future development of strategies that may improve neuronal transplantation therapies.

Disclosures: K. Huang: None. **A. Ho:** None. **C. Gomes:** None. **J. Meyer:** None. **M.A. Samuel:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.11/B5

Topic: A.04. Transplantation and Regeneration

Support: JSPS KAKENHI Grant 21K19690

Title: Gene expressions regulated by pharmacological inhibition of histone deacetylase in rat Schwann cell

Authors: *H. MAEJIMA[1], T. NISHIO[2], Y. DING[2], K. TSUTSUMI[3], Y. TAKAMATSU[1], T. MASAKI[4];
[1]Dept. of Rehabil. Science, Fac. of Hlth. Sci., [2]Grad. Sch. of Hlth. Sci., [3]Dept. of Biomed. Sci. and Engineering, Fac. of Hlth. Sci., Hokkaido Univ., Sapporo, Japan; [4]Ctr. for Med. Educ., Teikyo Univ. of Sci., Tokyo, Japan

Abstract: Transplantation therapy using Schwann cell has been focused on specifically in central nervous system (CNS) disorders such as spinal cord injury. Oligodendrocytes comprise myelin sheath in the CNS, whereas Schwann cells comprise it in the peripheral nerve system.

However, Oligodendrocytes express Myelin-associated inhibitor such as NOGO, MAG and OMgp against axonal regeneration. Thus, instead of oligodendrocytes, transplantation of Schwann cells to the injured CNS has been expected to contribute to myelination, axonal regeneration and remodeling of the CNS, accompanied by the expression of neurotrophic genes without expression of inhibitory molecules mentioned above. Histone acetylation is a potent epigenetic modification that is related to transcriptional regulation. Histone acetylation typically promotes gene expression. Thus, inhibition of histone deacetylases (HDACs) enhances histone acetylation globally, promoting gene expression. Pharmacological treatment using HDAC inhibitors (HADCis), which can enhance acetylation levels and increase anti-inflammatory and neurotrophic gene expression in the CNS, is expected to be a potential CNS conditioning method for neurorehabilitation. Therefore, targeting combined therapy of Schwann cell transplantation with pharmacological treatment using HDACi, we examined the effects of sodium butyrate (NaB), an HDACi on the gene expressions related to myelination, neuroprotection, neurotrophic function in addition to apoptosis in Schwann cell. Rat Schwann cells were cultured in the medium with NaB at different concentrations of 0, 0.1, 1.0, 5.0, 10.0 and 50mM for 24h, followed by the evaluation of cell viability. Subsequently, total RNA were collected from treated cells and cDNA was reverse-transcribed from isolated mRNA. Gene expression of neurotrophic factors (BDNF, GDNF and IGF-1), myelin-associated proteins (MBP and MPZ), and apoptosis marker (caspase-3) were assayed using real time PCR. Treatment with high concentration of 50mM NaB increased expression of caspase-3 and BDNF, and decreased cell viability. Meanwhile, treatment with lower concentration of 5.0mM NaB could increase IGF-1 expression, whereas 1.0mM NaB could increase the expressions of GDNF, MBP and MPZ, indicating that treatment with lower concentration of NaB could enhance myelin-associated protein and neurotrophic factors without apoptotic signaling. Altogether, this study suggests that it is important for transplantation therapy using Schwann cells to find a minimal and appropriate dose of HDACi enhancing beneficial gene expression related to myelination and neurotrophic function.

Disclosures: **H. Maejima:** None. **T. Nishio:** None. **Y. Ding:** None. **K. Tsutsumi:** None. **Y. Takamatsu:** None. **T. Masaki:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.12/B6

Topic: A.04. Transplantation and Regeneration

Support: EY029739

Title: Experimental upregulation of a novel developmentally downregulated micro RNA in retinal ganglion cells restores embryonic levels of mitochondria associated gene expression and promotes axon regeneration after injury in vivo

Authors: *W. C. THEUNE, A. LUKOMSKA, J. XING, M. P. FROST, E. F. TRAKHTENBERG;
Neurosci., Univ. of Connecticut, Farmington, Farmington, CT

Abstract: Central nervous system (CNS) projection neurons such as retinal ganglion cells (RGCs) do not spontaneously regenerate axons disrupted by injury or disease. RGC axons can be irreversibly damaged in optic neuropathies, which could be caused by optic nerve trauma, stroke, or glaucoma, and lead to loss of vision. Neuronal developmental capacity to grow long axons declines sharply after birth, and several factors that are themselves developmentally-regulated in RGCs were found to underlie the regenerative failure. No clinical treatments exist to date that could help patients with axonal injuries in the CNS to regenerate damaged circuits. Here, we identified a micro-RNA (miRNA; identity masked due to proprietary information) using small-RNA-seq of embryonic and mature purified RGCs, and investigated its role in RGC survival and axon regeneration after optic nerve injury, using a well-established murine *in vivo* model of optic nerve crush (ONC). We confirmed small-RNA-seq prediction of developmental-downregulation of the candidate miRNA by quantitative-PCR (qPCR), and also found that it is further downregulated in RGCs after ONC. Then, we pre-treated the RGCs with intraocularly injected AAV2 vector, which expressed either the candidate miRNA-mimic or a scramble shRNA (control), and performed ONC. At 2 weeks after injury, we evaluated the effects of the treatment on RGC survival and axon regeneration. We found that experimentally upregulating this miRNA promoted both RGC survival and axon regeneration. In order to characterize the mechanisms through which this miRNA elicited neuroprotection and promoted axon regeneration, we analyzed by bulk-mRNA-seq adult RGCs treated with AAV2 expressing miRNA-mimic or a scramble shRNA (control), and compared to bulk-mRNA-seq-analyzed transcriptome of purified embryonic and postnatal RGCs. These analyses led to the identification of a subset of genes, which were downregulated after treatment and whose levels were also upregulated during RGC maturation, consistent with developmental downregulation of the miRNA. Using miRNA target-prediction bioinformatic tools, several of these developmentally-upregulated genes were also predicted to be direct targets of the miRNA. Along with the genes downregulated by the treatment, we also found upregulated genes, which were presumed to be downstream of the mRNAs downregulated by the miRNA-mimic treatment, and were enriched for mitochondria-associated biological processes. Thus, a novel miRNA-regulator of RGC development and mitochondria-associated biological processes is a promising candidate for therapeutic neuroprotection and axon regeneration.

Disclosures: W.C. Theune: None. **A. Lukomska:** None. **J. Xing:** None. **M.P. Frost:** None. **E.F. Trakhtenberg:** None.

Poster

PSTR247. Regeneration in the CNS

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR247.13/B7

Topic: A.04. Transplantation and Regeneration

Support: RS-2023-00209591
HI20C0173

Title: Delivery of axon guidance gene-targeted siRNA nanoparticles via dual-degradable hydrogels improve cell proliferation of transplanted neural stem cells after spinal cord injury

Authors: *S. KIM[1], G. HAN[2], S. SOHN[3];
[1]CHA University, CHA Bundang Med. Ctr., Gyenggi-do, Korea, Republic of; [2]CHA University, CHA Bundang Med. Ctr., Gyunggi-do, Korea, Republic of; [3]neurosurgery, CHA University, CHA Bundang Med. Ctr., Gyeonggi-do, Korea, Republic of

Abstract: Neural stem cells (NSCs) derived from embryonic spinal cord are excellent candidates for cellular regeneration of lost neural cells after spinal cord injury (SCI). Semaphorin 3A (Sema3A) is well known that it is implicated in the major axon guidance of growth cone as a repulsive function during the central nervous system development, yet its function in the NSC transplantation therapy for SCI has not been investigated. Here, we first report that embryonic spinal cord-derived NSCs significantly expressed Sema3A in the SCI environment, which can inhibit cell proliferation after transplantation. Knockdown of Sema3A by delivering siRNA nanoparticles via dual-degradable hydrogels significantly induce to increase cell survival and neuronal differentiation of the transplanted NSCs after SCI. Of note, knockdown of Sema3A increase synaptic connectivity of transplanted NSC in the injured spinal cord. Moreover, extracellular matrix molecule and functional recovery were significantly improved in the Sema3A-inhibited rats compared to those in the NSCs transplanted-only rats. These findings show the important role of Sema3A in NSC transplantation therapy, which may be considered in future cell transplantation therapy for SCI.

Disclosures: S. Kim: None. **G. Han:** None. **S. Sohn:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.01/B8

Topic: A.07. Developmental Disorders

Support: NIH R01 NS088566
Bill and Melinda Gates Millennium Scholars Program
New York Stem Cell Foundation

Title: Characterizing contributions of maternal immune activation (MIA)- associated metabolites to embryonic brain development

Authors: *T. LACEY[1,2], B. PETROVA[3], S. GELB[3], N. KANAREK[3,4], M. LEHTINEN[5];
[1]Boston Children's Hosp. Pathology Dept., Harvard Univ., boston, MA; [2]Biol. and Biomed. Sci. PhD Program, Div. of Med. Sciences, Harvard Med. Sch., Boston, MA; [3]Pathology Dept.,

Boston Children's Hosp., Boston, MA; [4]Broad Inst. of Harvard and Massachusetts Inst. of Technol., Cambridge, MA; [5]Boston Children's Hosp. Pathology Dept., Harvard Med. Sch., Boston, MA

Abstract: Maternal immune activation (MIA) by viral, bacterial, or parasitic infection that results in hospitalization enhances the risk in offspring for neurodevelopmental disorders including autism spectrum disorders (ASD). During cerebral cortical development, neural progenitors first proliferate along cerebrospinal fluid (CSF)-filled ventricles and then differentiate into neurons and glia cells that form the cerebral cortex. The choroid plexus (ChP), an epithelial structure located in each brain ventricle, regulates CSF production and composition including by secreting instructive cues and nutrients for proper brain development and provides a critical brain barrier that help protect that brain from peripheral insults. Previously, our lab found that MIA in mice leads to a pro-inflammatory cytokine state in the embryonic CSF and accumulation of macrophages at the embryonic ChP. This led us to speculate that ChP-mediated nutrient secretion into the CSF is also perturbed in MIA and we tested this by thorough characterization of the changes in mouse embryonic CSF metabolome following MIA. Leveraging the quantitative power of liquid chromatography-mass spectrometry, we performed untargeted metabolomics and profiled MIA-induced changes in the embryonic CSF. This revealed elevation of glucocorticoids and kynurenine pathway related metabolites in embryonic CSF, validated by subsequent targeted metabolomics analyses. The kynurenine pathway is known to be associated with several neuropathologies, and its elevation following inflammation is in accordance with previous findings in adult CSF. Glucocorticoids, among the most prescribed drugs for the treatment of immune and inflammatory disorders, are known for their anti-inflammatory and immunosuppressive effects, and commonly repress the expression of cytokines in macrophages. Currently, we are interrogating the functional roles of glucocorticoids and kynurenine pathway metabolites on embryonic brain development. Our in-depth characterization of the mouse embryonic CSF should reveal mechanistic insights regarding causative abnormalities in CSF composition and inform future interventions / therapeutic strategies during MIA.

Disclosures: **T. Lacey:** None. **B. Petrova:** None. **S. Gelb:** None. **N. Kanarek:** None. **M. Lehtinen:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.02/B9

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 MH130600-01
NIH Grant R21 MH133014-01

Title: Strategies for the rescue of cellular and behavioral deficits in a NEXMIF-dependent mouse model of Autism spectrum disorder

Authors: *K. E. ODAMAH[1], H. MAN[1,2];
[1]Biol., Boston Univ., Boston, MA; [2]Pharmacol. & Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA

Abstract: We previously confirmed that loss of the X-linked gene NEXMIF results in Autism spectrum disorder (ASD) and intellectual disability. To study the neurobiological function of NEXMIF and its implication in ASD, we generated NEXMIF knockout (KO) male mice which display significant neuronal deficits and autism-like behaviors. As a proof-of-concept study, we utilized postnatal reintroduction of NEXMIF and its downstream genes as a strategy for rescuing the impaired cellular and behavioral phenotypes in KO mice. We find that injection of a NEXMIF lentivirus into KO mouse brains at postnatal day 1 (P1) rescues NEXMIF and synaptic protein expression, reduces anxiety, and improves preference for social novelty and novel object recognition memory by P30. Additionally, reintroduction of Filip1, a top gene transcriptionally regulated by NEXMIF, rescues impaired dendritic outgrowth in NEXMIF knockdown cortical neurons, indicating that gene reintroduction may serve as a rescue strategy in loss of NEXMIF conditions. Comparable to the majority of human female cases, our NEXMIF heterozygous (HET) female mouse model also shows autism-like behavioral impairments and defects in neuron morphology. During X chromosome inactivation (XCI) in early development, Xist RNA accumulates on the future inactive X chromosome (Xi), leading to its silencing. Because NEXMIF is an X-linked gene, random XCI results in mosaic NEXMIF expression in the HET brain: some neurons express wild-type (WT) NEXMIF, while other neurons completely lack NEXMIF (KO) and retain a silenced copy of WT NEXMIF on the Xi. Therefore, the silenced NEXMIF copy in the KO neurons of HET mice could potentially be expressed via X-chromosome reactivation. Indeed, we demonstrate that potent DNA methylation inhibitors can successfully reactivate NEXMIF from the Xi in cultured WT and HET female mouse cortical neurons. Moreover, injection of the inhibitors into WT and HET female mouse brains at P1 is sufficient to increase cortical NEXMIF expression by P15, which is still evident at P30. Overall, these findings lay the groundwork for further research aimed toward investigating the therapeutic potential of gene reintroduction and reactivation techniques in NEXMIF-dependent ASD.

Disclosures: K.E. Odamah: None. **H. Man:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.03/B10

Topic: A.07. Developmental Disorders

Support: NIMH 1R15MH118627-01
Vassar College internal research funds

Title: Maternal Fmr1 deficiency dysregulates offspring sociability and oxytocinergic signaling in the VTA

Authors: D. DUNN[1], E. TINCHER[1], M. RUSSELL[1], B. KHEYFETS[1], S. BOUKOBZA[1], G. COSTE[1], B. SULAMAN[1], J. KEE[1], K. NEWHALL[1], ***B. ZUPAN**[2];
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Abstract: Impaired social interaction is a core dimension of neurodevelopmental disorders. Neuropeptide oxytocin (OXT) signaling in the VTA is critical for mediating rewarding aspects of social behavior. Specifically, OXT modulates activity of VTA dopamine neurons whose projections to the NAc bidirectionally modulate duration of social interaction. The mouse model of Fragile X Syndrome (FXS) exhibits abnormal sociability, and our research suggests that this phenotype is programed in part by maternal *Fmr1* deficiency. We've reported that haploinsufficiency of maternal *Fmr1* (*Fmr1*$^{+/-}$) is sufficient to induce hypersociability in genetically normal (wild-type (WT); *Fmr1*$^{+/y}$) male offspring, indicating developmental sensitivity to maternal FMRP levels. We've also reported that intranasal (IN) OXT administration increases sociability in WT controls, but not in hypersocial mice, actually decreasing social interaction in WT mice from FMRP deficient dams. Here, we asked whether maternal FMRP-programmed sociability is associated with dysregulated OXT signaling in the VTA. We found that IN OXT increases VTA cfos expression and sociability in control mice, confirming that IN OXT modulates activity in this brain region. Interestingly, blocking VTA OXT receptors (R) with a highly selective antagonist prior to IN OXT administration failed to block OXT-mediated increase in social interaction. Rather, it mimicked it - intra-VTA administration of the antagonist increased social interaction time and decreased avoidance of a novel conspecific. We then administered OXT directly into the VTA and found that, like IN administration, intra-VTA OXT increased sociability and decreased avoidance in WT control mice, but failed to modify sociability in maternal FMRP-programmed mice. Varying doses of atosiban, another OXTR antagonist, blocked OXT-mediated effects on sociability in WT control, but had no effect on social behavior in maternal FMRP-programmed WT mice. We found no differences across groups in the number of OXT+ neurons in the PVN nor in the number of PVN neurons innervating the VTA. A semiquantitative fluorescence in situ hybridization analysis of OXTR gene expression in dopaminergic and GABAergic neurons of the VTA also revealed no differences across groups. In sum, our data shows that the lack of oxytocin-induced effects on sociability in maternal FMRP-programmed mice is not mediated by altered OXT innervation of the VTA or OXTR expression in this region. Rather, it suggests that dysregulated oxytocinergic signaling is mediated by a functional deficit in OXTRs, although we cannot yet exclude the possibility of an arginine vasopressin receptor-mediated effect.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.04/Web Only

Topic: A.07. Developmental Disorders

Support: 255317 CONACYT
708452 CONACYT
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PAICYT 2020
IBRO-LARC 2020

Title: Mcp-1 signaling disrupts social behavior by modulating brain changes and microglia morphology

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Abstract: Autism spectrum disorder (ASD) is a disease characterized by reduced social interaction and stereotypic behaviors and related to macroscopic volumetric changes in cerebellar and somatosensory cortices (SPP). Epidemiological and preclinical models have confirmed that a proinflammatory profile during fetal development increases ASD susceptibility after birth. Here, we aimed to globally identify the effect of maternal exposure to high-energy dense diets, which we refer to as cafeteria diet (CAF) on peripheral and central proinflammatory profiles, microglia reactivity, and volumetric brain changes related to assisting defective social interaction in the mice offspring. We found a sex-dependent effect of maternal exposure to CAF diet or inoculation of the dsARN mimetic Poly (I:C) on peripheral proinflammatory and social interaction in the offspring. Notably, maternal exposure to CAF diet impairs social interaction and favors an increase in anxiety in male but not female offspring. Also, CAF diet exposure or Poly (I:C) inoculation during fetal programming promote peripheral proinflammatory profile in the ASD-diagnosed male but not in females. Selectively, we found a robust accumulation of the monocyte chemoattractant protein-1 (MCP-1) in plasma of ASD-diagnosed males exposed to CAF during fetal development. Biological assessment of MCP-1 signaling in brain confirms that systemic injection of MCP-1-neutralizing antibody reestablished social interaction and blocked anxiety, accompanied by a reduction in cerebellar lobule X (CbX) volume and an increase volume of the primary somatosensory (SSP) cortex in male offspring. These data highlight the contribution of diet-dependent MCP-1 signaling on volumetric brain changes and microglia morphology promoting ASD-like behavior in male mice.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Topic: A.07. Developmental Disorders

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Title: Altered excitatory/inhibitory balance in the prefrontal cortex of a mouse model of autism: from neuronal excitability to cerebellar modulation in vivo.

Authors: *D. DI DOMENICO[1], E. PALI[1], M. CONFORTI[1], T. SODA[1], I. MONTAGNA[1], S. TRITTO[1], E. D'ANGELO[1,2], F. PRESTORI[1], L. MAPELLI[1];
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Abstract: Autism spectrum disorders (ASD) are characterized by altered social interaction and repetitive behavior and are supposed to affect prefrontal cortex and cerebellum. IB2 KO mice provide a good ASD model, since the human IB2 orthologous gene is usually co-deleted with SHANK3 in the Phelan-McDermid syndrome. Here, we characterized the prelimbic cortex (PrL) activity and its control by cerebellar stimulation in IB2 KO and WT mice. *In vivo* single unit (SU) recordings of putative PrL pyramidal neurons were performed to characterize spontaneous activity and responses to electrical stimulation of the cerebellar dentate nucleus (DN) under urethane anesthesia (in 13 KO and 15 WT SUs). IB2 KO SUs showed lower basal frequency (KO=0.7±0.1Hz, WT=1.1±0.1Hz; p=0.03) and a reduced response to DN stimulation (KO=-2.5±0.3sp/bin, WT=-3.5±0.3sp/bin; p=0.06). Local superfusion of dopaminergic D1 and D2-like receptor blockers (SCH23390 and Sulpiride) either decreased or increased the basal firing rate, compatible with the heterogeneous distribution of D1/D2-like receptors in PrL pyramidal neurons, with no significant differences between WT and KO. The interplay between the GABAergic and dopaminergic systems was evident in the correlation between the effects of GABA-A (with SR95531) and D1/D2-like receptors blockade, that was investigated by sequentially blocking D1/D2-like and GABA-A receptors. Importantly, inhibition block had a stronger impact on KO than WT, both on basal firing rate (KO=417±128%, WT=157±53%; p=0.04) and on responses to DN stimulation (KO=420±118%, WT=165±68%; p=0.005). Since

the blockade of inhibition revealed an hyperexcitability of IB2 KO pyramidal neurons, *ex vivo* experiments were performed to get deeper insight on neuronal and local microcircuit changes. Voltage sensitive dye imaging in acute PrL slices revealed an increased excitatory/inhibitory (E/I) balance in KO, characterized by larger excitation cores (KO=399±41µm, WT=246±28µm; p=0.02) with little lateral inhibition in PrL columns. Accordingly, whole-cell patch-clamp recordings of layer V pyramidal neurons showed a significantly increased excitability of KO neurons, an upward shift in the frequency/intensity plot (KO=11.2±1.2Hz, WT=4.7±2.2Hz; p=0.03), and a larger inward current density. While the experimental assessment of D1/D2-like and GABA-A receptors functions *ex vivo* is ongoing, our preliminary results suggest that PrL neurons hyperexcitability might be compensated *in vivo* by mechanism boosting inhibitory modulation. Further investigations are warranted to investigate the balance between primary and compensatory changes in the PrL of IB2 KO mice.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Program #/Poster #: PSTR248.06/B12

Topic: A.07. Developmental Disorders

Support: NIH Grant GR107695

Title: The role of autism-associated postsynaptic density SHANK2 protein in modulating novelty-induced arousal transitions

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Abstract: Organisms strategically use internal states and external information to execute differential behaviors and state transitions depending on specific contexts. Arousal states, in particular, are known to be essential for survival and adaptation in response to sensory input, emotional burden, physiological needs, and changes in the environment. Although previous studies have suggested that the anterior cingulate cortex (ACC) maintains sustained arousal in novel environments and is involved in attentional-state switching, the mechanisms by which neural ensembles and molecular networks mediate arousal states are not well understood. SHANK2 is a scaffolding protein located at the postsynaptic density of excitatory neurons that is involved in synaptic regulation through the formation and stabilization of synapses during development. SHANK2 is predominantly expressed in the cortex with high expression in the ACC. In this study, we sought to investigate the role *SHANK2* plays in modulating novelty-induced arousal using the *Shank2* complete knockout mouse model with a deletion of exon 24 (*Shank2*Δe24). To assess novelty-induced arousal, we developed a modified behavioral paradigm

where mice are challenged with a Novelty-Habituation-Novelty scheme. We found that most mice, regardless of genotype, extensively explore an object on the first day of exposure. *Shank2*$^{\Delta e24-/-}$ mice spend significantly more time exploring and interacting with the object after initial and repeated exposures. These data suggest that *Shank2*$^{\Delta e24-/-}$ mice have an increased arousal response to novelty and a persistent interest in familiar objects. Yet, this response is not due to a long-term or short-term memory impairment since *Shank2*$^{\Delta e24-/-}$ mice have a normal novelty recognition index at both a 5min and 24h recall. Due to the role of the ACC in modulating novelty-related behaviors and arousal, we sought to remove *Shank2* from this region using the *Shank2* conditional knockout line (*SHe24*^{flox}). Our preliminary data suggest that ACC-Cre mice have an increased arousal response toward a novel object evidenced by significantly more time spent exploring the object and an increased number of interactions. Taken together, our data suggest that *Shank2* in the ACC may play an important role in achieving an appropriate arousal response toward novelty. Future work using fiber photometry and circuit manipulation techniques to evaluate 1) how the lack of *Shank2* affects the neural dynamics of the ACC and 2) how *Shank2* might mediate appropriate novelty-induced arousal state transitions.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Summer Physiology Undergraduate Researcher Program (SPUR R25-NS115552)
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San Antonio ISD Summer Research Program at UT Health San Antonio

Title: Amantadine Has Efficacy to Reduce Restrictive-Repetitive Behavior in BTBR Mice

Authors: *S. GREENE[1], G.-A. ALCALA[2], A. ONTANON[3], A. C. SHAKOCIUS[4], I. PARK[3], E. REED[3], A. JOHNSON[3], I. BUSTAMANTE[3], M. SCHILLERSTROM[3], B. GINSBURG[4], G. GOULD[5];
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Abstract: The goal of this study was to determine if the drug amantadine, usually used to control some viral infections and dyskinesia in Parkinson's disease, would have any efficacy to reduce

the restrictive-repetitive behaviors characteristic of autism spectrum disorders (ASD). Males of the inbred strain BTBR typically bury lots of marbles relative to male C57BL/6J but this behavior in females is less well characterized. The study hypothesis was that sub-chronic amantadine treatment would be more effective than acute treatment, and higher doses would be more effective than lower doses to reduce marble burying. Mice, both male and females, were used as subjects, and the drug was injected daily at a dose of 50 or 150 mg/kg for 6 days. These doses resulted in steady state serum levels of (mean ± S.E.M.) 260 ± 58 and 693 ± 40 ng/ml amantadine, respectively. Ten each male and female mice per dose of amantadine were tested for marble burying on Day 1 and again on Day 6. On Day 1, male BTBR buried more marbles than female BTBR mice, but on Day 6 this difference was not evident because control females were burying more marbles. In both males and females, amantadine at a dose of 150 mg/kg/day reduced marble burying significantly relative to the control treated groups. Overall, amantadine may be useful to ameliorate restrictive-repetitive behaviors that occur in autism and other psychiatric disorders, a purpose different from its current use to reduce dyskinesia.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Topic: A.07. Developmental Disorders

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Brain & Behavior Research Foundation NARSAD 28298
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Title: Modulation of the maternal gut microbiome with probiotics during pregnancy prevents autism-like phenotypes in environmental and idiopathic mouse models

Authors: *I. J. BOLDING[1,2], L. M. MATZ[1,2], C. M. DI GESU[5], R. FULTZ[6], K. L. HOFFMAN[3,4], J. F. PETROSINO[3,4], S. A. BUFFINGTON[1,2];
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Abstract: Disruption of the maternal gut microbiome during pregnancy is associated with adverse neurodevelopmental outcomes. We previously showed that maternal high-fat diet (MHFD) in mice induces gut dysbiosis and social dysfunction in male and female offspring across two generations (F_1, F_2), and that supplementation of offspring drinking water with *Limosilactobacillus* (*L.*) *reuteri* upon weaning rescues social dysfunction and selectively remodels the female gut microbiome by promoting expansion of short-chain fatty acid (SCFA)-producing taxa. We hypothesized that targeted remodeling of the maternal gut microbiome during pregnancy would improve neurobehavioral outcomes in offspring born to obese dams. We therefore developed a maternal probiotic cocktail (MPC) consisting of seven immunomodulatory taxa and administered it to maternal regular diet (MRD) control and HFD-fed dams during pregnancy and lactation. Antenatal targeting of the maternal gut microbiome was sufficient to restore neurotypical social behavior of male and female MHFD + MPC lineage offspring (F_1) compared to MHFD lineage offspring, demonstrated by restored sociability and preference for social novelty in Crawley's three-chamber assay, and increased number of contacts and interaction times in the reciprocal social test for MHFD + MPC male and female offspring, respectively. Importantly, probiotic treatment of MRD controls displayed normative behavior. Metataxonomic 16S rRNA gene amplicon sequencing of stool collected from MHFD and MHFD + MPC lineages revealed few changes in alpha diversity, suggesting that MPC produces functional changes that prevent the onset of autism-like phenotypes in offspring born to HFD-fed mice. Thus, we performed metabolomics of dam and offspring serum and stool, revealing significant fold changes in the MHFD + MPC lineage compared to the MHFD lineage including changes in bile acids, carbohydrate utilization, and fatty acid synthesis and metabolism. Collectively, these results suggest that increasing biosynthetic potential for SCFAs through probiotic supplementation results in an improved serum metabolome, and that therapeutic targeting of the maternal gut microbiome may represent a promising strategy to lower neurodevelopment risks associated with in utero environmental exposures including infection, overnutrition, and particulate matter. We are currently testing the efficacy of a maternal probiotic in genetic and idiopathic mouse models for ASD. Our results link the maternal lineage to instability of descendant microbial communities and maladaptive social behavior and highlight the interaction between host genetics and host microbiota.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Program #/Poster #: PSTR248.09/B15

Topic: A.07. Developmental Disorders

Support: Departmental startup funds.

Title: Cntnap2 affects conditioned fear memory during early development

Authors: *H. JANOUSCHEK, R. J. TAUGHER-HEBL, A. BERNS, A. TOWNSEND, A. K. EAGEN, M. JONES, H. STEVENS, D. LANGBEHN, J. WEMMIE;
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Abstract: The circuitry that underlies Pavlovian fear conditioning has been suggested to undergo marked changes during brain development. During rodent late pre-weaning and early post-weaning period, these changes include alterations in several molecular mechanisms underlying synaptic plasticity and neuron morphology. The contactin-associated protein-like 2 (CNTNAP2) is a neurexin, which has been associated with neurodevelopmental disorders, synapse formation and stabilization. It is highly expressed in the limbic circuitry, including the amygdala and the hippocampus. Therefore, it is feasible that CNTNAP2 differentially affects fear learning or fear memory recall during brain development. To explore this possibility, we tested Pavlovian fear conditioning in 18-day-old (P18) wildtype (*Cntnap2*$^{+/+}$) mice and *Cntnap2* deficient (*Cntnap2*$^{-/-}$) littermate controls. We then tested cue-evoked freezing and its persistence in the same cohort of mice using mixed effects linear regression analyses. P18 *Cntnap2*$^{-/-}$ mice didn't differ significantly from their *Cntnap2*$^{+/+}$ littermates during fear conditioning. However, knockout mice performed significantly worse on cue-evoked freezing 24 hrs. after training. Interestingly, 1 to 2 weeks later, the persistence of cue-evoked freezing in *Cntnap2*$^{+/+}$ mice declined more than in *Cntnap2*$^{-/-}$ mice, largely eliminating the genotype difference, and suggesting that although memory was initially impaired in the *Cntnap2*$^{-/-}$ mice, it may be more stable. Previous studies suggested CNTNAP2 is involved in spine stability in adult animals. Therefore, one potential explanation for our results might be genotype differences in spine stability which is a future direction for investigation. Together these data provide the first evidence for CNTNAP2 dependent effects on Pavlovian fear conditioning early during development.

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Poster

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Topic: A.07. Developmental Disorders

Support: MRC Grant MR/V013173/1 to AB

Title: Neurodevelopmental functions of the histone demethylase KDM5B

Authors: *L. PÉREZ SISQUÉS[1], S. BHATT[1], A. CARUSO[5], M. U. AHMED[1], T. GILEADI[1], J. TAYLOR-PAPADIMITRIOU[2], A. PITTMAN[6], M. SCATTONI[5], P. GIESE[3], C. FERNANDES[3], A. BASSON[1,4,7];
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Abstract: Loss of function mutations in genes encoding lysine methyltransferases responsible for trimethylation of histone 3 on lysine 4 (H3K4me3), H3K4me3 readers and demethylases are associated with a range of neurodevelopmental conditions, including autism spectrum disorder (ASD) and intellectual disability (ID). *KDM5B* mutations have been reported in patients with ASD, ID and developmental delay. Many of the ASD-associated mutations identified in *KDM5B* are within or around the catalytic domain of the protein, implicating H3K4me3 demethylase activity in ASD pathogenesis. We hypothesized that a deficiency in the demethylation activity of KDM5B will lead to a dysregulated H3K4me3 epigenome, abnormal neurodevelopmental gene expression and ASD-like behaviours in mice. We obtained a mouse line, *Kdm5b*$^{\Delta ARID/\Delta ARID}$, with a deletion of exons 2-4, resulting in reduced KDM5B protein with a complete loss of demethylase activity. Homozygous mice exhibited increased brain-to-body weight ratios, suggesting neurodevelopmental defects. To investigate the in vivo function of the protein in the developing brain, H3K4me3 levels were measured in the neocortex of postnatal day 5 (P5) mice by western blot. H3K4me3 levels were significantly increased, compared to wildtype (WT) littermates. Next, we investigated whether homozygous mice showed ASD-associated behavioural phenotypes. We observed reduced ultrasonic vocalizations in juvenile mutant mice. Adult mice did not show differences in socio-communicative or anxiety behaviours, but mutant mice displayed increased repetitive behaviours and reduced performance on the accelerating Rotarod. High resolution structural MRI revealed volumetric alterations in adult mutant mice compared to WT littermates . Finally, we confirmed by RNAseq that the increased H3K4me3 levels observed in *Kdm5b*$^{\Delta ARID/\Delta ARID}$ mice resulted in altered gene expression in the neocortex. The top biological pathways affected in mutant samples included developmental and signalling-associated genes. In conclusion, our results indicate that the lack of KDM5B demethylase activity leads to altered levels of H3K4me3, neurodevelopmental phenotypes and dysregulated gene expression in the neocortex.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Neubauer Family Foundation

Title: The NO Answer for Autism Spectrum Disorder

Authors: *M. K. TRIPATHI[1], S. K. OJHA[1], M. KARTAWY[1], W. HAMOUDI[1], A. CHOUDHARY[2], S. STERN[2], A. ARAN[3], H. AMAL[1];
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Abstract: Autism spectrum disorders (ASDs) include a wide range of developmental disorders that share a core of neurobehavioral deficits manifested by abnormalities in social interactions, deficits in communication, restricted interests, and repetitive behaviors. Several reports showed that mutations in different high-risk ASD genes, including SHANK3 and CNTNAP2, lead to ASD. However, the underlying molecular mechanisms have not been deciphered, and no effective pharmacological treatment has been established for ASD. Recently, we reported a dramatic increase in nitric oxide (NO) levels in different ASD mouse models. NO is a multifunctional neurotransmitter that plays a key role in different neurological disorders. However, its functional role in ASD has not yet been fully investigated. Here, we conducted a multidisciplinary comprehensive study using cellular and mouse models, as well as clinical samples and human iPSCs to investigate the role of NO in ASD. Our study showed that treating wild-type mice with an NO donor led to an ASD-like phenotype, which has been confirmed biochemically and behaviorally. High levels of nitrosative stress biomarkers were found in the cortex and the striatum of both the Shank3 and Cntnap2 ASD mouse models. Pharmacological intervention with a neuronal NO synthase (nNOS) inhibitor in both models reversed the molecular, synaptic, and behavioral ASD-associated phenotypes. These findings were validated in primary neuronal cultures as well as genetically in Shank3 and nNOS double-knocked down human SHSY5Y cells. Importantly, treating iPSC-derived cortical neurons from patients with SHANK3 mutations with the nNOS inhibitor showed similar therapeutic effects. Clinically, we found a significant increase in nitrosative stress biomarkers in the plasma of low-functioning ASD patients, compared with typically developed volunteers. An innovative mass spectrometric method, SNOTRAP, was utilized to identify the S-nitrosylated proteins to identify NO-mediated post-translational modifications in the clinical plasma samples. Bioinformatics revealed that the complement systems as well as the synaptic and neuronal development processes were enriched in the ASD group. This novel work reveals that NO plays a significant role in ASD development. Our important findings will open future and novel directions to examine NO in diverse mutations

on the spectrum as well as in other neurodevelopmental disorders and psychiatric diseases. Finally, it suggests a novel strategy for effectively treating ASD.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Topic: A.07. Developmental Disorders

Support: UF1NS111692
R01NS076708

Title: Autism-associated KCND2 mutation induces multiple behavioral abnormalities in heterozygous knock-in mice

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Abstract: The *KCND2* gene encodes the Kv4.2 voltage-gated potassium channel that forms the somatodendritic subthreshold A-type current (I_{SA}) important for regulating membrane excitability, repetitive firing, action potential backpropagation, and signal integration and processing. A missense mutation in KCND2 (Kv4.2/V404M) was identified in patients with early-onset epilepsy, autism, and global developmental delay (Lee et al, 2014; Zhang et al, 2021); however, a direct link between the V404M mutation and the disease phenotype has not been firmly established. To investigate the potential role of the V404M mutation in disease etiology, we generated heterozygous V404M knock-in C57BL/6J mice using CRISPR technology and observed their development and behavior in comparison against age-matched and sex-matched wild-type controls (male and female: wild-type, n=5 each; V404M, n=4 or 5 each). The V404M heterozygotes exhibit marked mortality during early development (~50% mortality), decreased body weight of males (25-30%), and a myriad of behavioral changes. In the open field assay, V404M mice display notable anxiety with hyperactivity (increased moving time: male, $p < 0.01$; female, $p < 0.01$) (greater distance traveled: male, $p = 0.03$, female, $p < 0.01$) and prominent thigmotaxis (increased margin time: male, $p < 0.01$; female, $p = 0.05$). In a conditioned fear (CF) assay, 24 hours after two rounds of training, V404M mice show little to no freezing response to the same environmental context (male, $p = 0.035$; female, $p = 0.01$) and

reduced response to the cued tone (male, $p = 0.01$; female, $p = 0.01$). In a Morris's water maze (MWM) assay, after four days of training mice were tested for their ability to remember the location of the hidden platform. In the MWM probe trials, V404M mice display thigmotaxis with undirected search behavior and spend less time in the platform zone compared to wild-type mice (male, $p = 0.05$; female, $p < 0.01$). Finally, male V404M mice show significantly reduced interest in social interactions in 3-chamber Crawley test (decreased partner cup time, $p = 0.02$). In conclusion, our results indicate that the V404M mutation produces a spectrum of behavioral changes in mice that likely have important implications for understanding the human disorder.

Disclosures: H.H. Jerng: None. **P.J. Pfaffinger:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.13/B19

Topic: A.07. Developmental Disorders

Support: NIH (mGAP: R24OD021324)

Title: Evolutionary constraint genes implicated in neurodevelopmental disorders across 2,054 rhesus macaque genomes

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Abstract: Significant progress has been made in understanding the genetic basis of neurodevelopmental disorders (NDDs), which are chronic, childhood-onset conditions that affect cognition, communication, and behaviour. These disorders are among the most severe from a public health perspective, and it is hoped that further research will lead to new therapeutic and intervention strategies. However, there are still significant gaps in our understanding of the link between genotype, neurobiology, and clinical phenotype, which means that new models are needed to advance our understanding. Rhesus macaques (*Macaca mulatta*) have been extensively used for preclinical neurobiological research because of their remarkable similarities to humans in neurobiology and sophisticated social and cognitive behaviours that cannot be captured by other experimental animals. Consequently, nonhuman primates offer the opportunity to understand the neurobiology of NDDs. We used the macaque Genotype And Phenotype (mGAP) resource (v2.0), which consists of 2,054 macaque genomes, to examine patterns of evolutionary constraint in known human neurodevelopmental genes. Residual variation intolerance scores (RVIS) were calculated for all annotated autosomal genes (N=18,168) and Gene Set Enrichment Analysis (GSEA) was used to examine patterns of constraint across the neurodevelopmental genes. We demonstrated that the patterns of constraint across autosomal genes are positively

correlated in humans and macaques (Pearson's product-moment correlation = 0.42, *P* = 2.2e-16), and those genes implicated in autism spectrum disorder (ASD), epilepsy, intellectual disability (ID) and schizophrenia (SZ) all exhibit significant constraint as evidenced by both GSEA and their significant over-representation among the top 2% constrained genes. Moreover, a small number of key NDD genes that are highly intolerant to mutation in humans showed no evidence of similar intolerance in macaques (*CACNA1D*, *CNTNAP2*, *MBD5*, *AUTS2* and *NRXN1*). The presence of pathological mutations in NDD genes among macaques, and the evidence of similar constraints in these genes to humans, provide a strong rationale for further investigation of genotype-phenotype relationships in nonhuman primates. This highlights the importance of identifying phenotypic behaviours associated with clinical symptoms, elucidating the neurobiological underpinnings of neurodevelopmental disorders, and developing primate models for translational neuroscience research to advance approaches for precision medicine and gene therapy interventions.

Disclosures: M. Woodbury-Smith: None. **M. Uddin:** None. **J. Veltman:** None. **Y. Kikuchi:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.14/B20

Topic: A.07. Developmental Disorders

Title: Preclinical study of deep brain stimulation for severe self-injurious behaviors associated with Autism Spectrum Disorder

Authors: *K. ZHANG[1,4], R. MATIN[1,4], M. EBDEN[1], C. GORODETSKY[2], F. VENETUCCI GOUVEIA[1], G. M. IBRAHIM[3,4];
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Abstract: Intractable self-injurious behaviour (SIB) is common in children with Autism Spectrum Disorder (ASD) with limited treatment options. Severe SIB is associated with physical injury, distress, repeated hospitalizations and reduced quality of life for children and their caregivers. Deep brain stimulation (DBS) - a neurosurgical procedure that involves implantation of electrodes and delivery of electric current into specific brain targets to therapeutically alter neural function - is an emerging treatment option for severely affected children. SIB is thought to result from dysfunctions in structures along the fronto-limbic-striatal network, thus, targeting these areas with DBS may reduce the severity and/or frequency of SIB. Neuromodulation within the fronto-limbic-striatal network has been successful in alleviating symptoms of SIB; however, the neural underpinnings of this treatment are poorly understood. Preclinical studies are required to better understand its mechanisms of action. The inbred BTBR T+ Itpr3tf/J (BTBR) mouse strain is commonly used for investigations of ASD as these mice display distinctive phenotypic

traits that constitute a reliable face-validity for modeling SIB and ASD. Notably, they exhibit excessive repetitive self-grooming; a behaviour that is comparable to SIB. To explore the effects of DBS of the fronto-limbic-striatal network on SIB and autism-relevant phenotypes, we used the BTBR mouse model of ASD and administered chronic high-frequency stimulation via implanted electrodes. Animals were tested for: I) excessive self-grooming, II) general locomotion and anxiety (open field test), III) socialization (three-chambered social approach test), and IV) repetitive behaviour (marble burying test). Neurocircuitry influenced by DBS of the fronto-limbic-striatal network was assessed using high-resolution magnetic resonance imaging. The chronic DBS treatment reduced injurious self-grooming and repetitive behaviours. Using deformation-based morphometry and MAGeTbrain (Multiple Automatically Generated Templates Brain Segmentation Algorithm) pipelines, we observed distinct volumetric changes along the neurocircuitry involved in regulating SIB. These preclinical results with mouse models of ASD provide insights into the plasticity induced by chronic high-frequency stimulation of the fronto-limbic-striatal network and has high translational potential.

Disclosures: K. Zhang: None. **R. Matin:** None. **M. Ebden:** None. **C. Gorodetsky:** None. **F. Venetucci Gouveia:** None. **G.M. Ibrahim:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Program #/Poster #: PSTR248.15/B21

Topic: A.07. Developmental Disorders

Support: NRF 2020M3E5D9080791
NRF 2016R1D1A1B02010387

Title: Integrated cortical and serum proteomic analysis of mice and patients exhibiting autism spectrum disorder (ASD) revealed the potential involvement of hemostasis, amino acid transport, and iron metabolism in ASD-like phenotype

Authors: *L. SAYSON[1], H. LEE[1], N. CAMPOMAYOR[2], S. BALATARIA[1], M. KIM[2], E. C. YI[3], B.-N. KIM[4], H. KIM[1], J. CHEONG[5];
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Abstract: The earliest diagnosis of autism spectrum disorder (ASD) dates back for over several decades. Nevertheless, the etiology of ASD development is still poorly understood, given its complexity as a multi-symptomatic behavioral disorder. Some transgenic mice models, such as the *Cntnap2* knockout (KO) mice, have exhibited ASD-like phenotypes in animal sociability paradigms, imparting valuable insights on ASD pathophysiology. This may provide an

opportunity for identifying detectable protein-based biomarkers, which may contribute to the development of early-onset ASD diagnostic methods. Herein, we performed an integrated approach for analyzing blood and brain proteomes from *Cntnap2* KO mice and/or patients diagnosed with ASD. Furthermore, functional enrichments and protein-protein interactions (PPIs) were determined through gene ontology (GO) and pathway analysis. 91 common differentially expressed proteins (DEPs) were determined between the proteomes obtained from *Cntnap2* KO mice and ASD patient blood. GO and pathway analysis revealed that hemostasis-related mechanisms were highly enriched in these DEPs. Comparison of the hemostasis-related proteome subset obtained from blood with published cortical proteomes of *Cntnap2* KO mice revealed that Filamin-A (FLNA) and Transferrin (TRF) were commonly upregulated and 4F2 cell-surface antigen heavy chain (SLC3A2) was commonly downregulated across the datasets. Mutations and/or dysregulations in genes that code FLNA, TRF, and SLC3A2 were previously found to potentially result in adverse neurodevelopmental consequences. Previous studies showed that mutations in *Flna* may influence SHANK3 (SH3 and multiple ankyrin repeat domains 3), whose mutation may also result in ASD-like phenotype in mice, while abnormal iron metabolism due to *Trf* dysregulation was found in autistic children. Reports describing the deletion or mutation of *Slc7a5* (solute carrier transporter 7a5), which encodes LAT1 (large neutral amino acid transporter 1) that can heterodimerize with SLC3A2, revealed ASD-like phenotypes in both mice and humans, including the detection of *Slc3a2* genetic variants in ASD patients. Further studies are currently underway that are geared towards the validation of these DEPs in other ASD animal models by correlating their expression levels with ASD-like phenotypes. Overall, our preliminary findings may further support the probable roles of neural and peripheral mechanisms associated with hemostasis, amino acid transport, and iron metabolism in the occurrence of ASD, rendering FLNA, SLC3A2, and TRF as potential biomarkers for early-onset ASD diagnosis.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.16/B22

Topic: A.07. Developmental Disorders

Support: PTEN foundation

Title: Phenotypic Rescue via mTOR inhibition in neuron specific PTEN knockout mice

Authors: *A. D'AMORE, M. SUNDBERG, R. LIN, E. LUBBERS, H. HING CHEONG LEE, M. SAHIN;
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Abstract: BACKGROUND: Germline *PTEN* mutations are commonly associated with PTEN Hamartoma Tumor Syndrome (PHTS), characterized by benign tumor-like malformations in the body. PHTS exhibits high rate of neurological comorbidities, including ASD, however the relevance of neuronal *PTEN* mutations in PHTS remains unclear. In this study, we: 1) generate *Synapsin-1^{Cre};PTEN$^{f/f}$* (Syn-PTEN KO) mice, 2) characterize this line's development, including survival and transcriptomic analyses, 3) generate and characterize Syn-PTEN KO mouse primary neuronal cultures, and 4) treat with Everolimus to test for phenotypes rescue.
METHODS: We crossed *PTEN$^{f/f}$* and *Synapsin-1^{Cre}* to generate Syn-PTEN KO mice. We measured body weight, brain:body weight ratio and survival of the resultant litters in all genotypes (HOM, HET, WT). Everolimus (3mg/kg, IP) was administered to HOM mice starting at P7, 3x/week. Western blot and RNA-seq were performed on brain tissue. Primary neuronal cultures were dissected from E18.5 pups and firing activity parameters were measured at baseline and post-treatment using the MEA system. Immunostaining for Synapsin1/PSD95/MAP2 expression was performed to quantify synapses in vitro.
RESULTS: We found significant reduction in body weight and lifespan and increased brain:body weight ratio in HOM mice compared to HET or WT control. Everolimus improved lifespan but not weight of HOM mice. HOM neuronal cultures showed increased weighted mean firing
rate and number of bursts compared to HET or WT controls. This network hyperactivity phenotype was partially rescued with everolimus. Synapsin1 and PSD95 were significantly increased on MAP2 neurites in HOM neurons, and were rescued upon everolimus treatment. RNA-seq revealed ~600 differentially regulated genes in HOM mice compared to control. Gene ontology analyses indicated myelin and extracellular matrix (ECM) are amongst the major subclasses of upregulated genes. Immunostaining confirmed significant increase in myelin and perineuronal nets in HOM mice.
CONCLUSION: We successfully generated a novel neuronal-specific PTEN knock-out mouse model. Syn-PTEN KO mice exhibited profound neurological and molecular pathology culminating in premature lethality. Everolimus only partially rescued these phenotypes. Primary HOM neuronal cultures demonstrated hyperactive firing properties as well as excitatory synaptic marker increase, and both were partly rescued by Everolimus. Our data suggests that mTOR inhibition only provides partial rescue of PTEN pathology, likely due to downstream targeting. Alternative approaches targeting upstream of mTOR might be tested in the future.

Disclosures: A. D'Amore: None. **M. Sundberg:** None. **R. Lin:** None. **E. Lubbers:** None. **H. Hing Cheong Lee:** None. **M. Sahin:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.17/B23

Topic: A.07. Developmental Disorders

Title: Behavioral comparison of the BTBR mouse model of autistic-like behavior against normo-social C57Bl/6J mice

Authors: U. DATTA[1], ***T. HEIKKINEN**[1], T. BRAGGE[1], R. DE FEO[1], M. DUDEK[1], K. MCCULLOUGH[2], P. PINE[2];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that manifests as impairments in social interactions, and restricted repetitive patterns of behaviors, interests, or activities. According to 2020 CDC estimates, U.S. reported ASD diagnosis in 1/36 children. The ability to identify therapeutic strategies to target the disease relies heavily on the existence of animal models that capture the disease phenotype. The BTBR T+ Itpr3tf/J mouse has been proposed as an idiopathic model of ASD. We compared male BTBR and C57BL/6J mice (n=12/group) aged 8-10 weeks, on a battery of behavioral tests (open field, Y-maze, self-grooming, reciprocal social interaction, marble burying) and using *in vivo* 1H-magnetic resonance spectroscopy (MRS). Memantine, a therapeutic agent proposed for the treatment of core symptoms of ASD, with previously demonstrated efficacy in this model was used as a reference compound.
Our findings revealed no significant differences in activity measures during the Open field assay, between the BTBR and C57 mice. In the Y-maze test for spatial reference memory, vehicle treated C57 mice displayed increased preference for the novel arm relative to the familiar arm, an outcome that was not observed for BTBR mice. In the self-grooming assay, the BTBR mice spent more time grooming compared to C57 mice. During social interaction test that quantified both social and non-social behavior, no clear deficit in social behavior was observed for BTBR mice. Among nonsocial behaviors, exploration was higher in vehicle treated BTBR mice compared to their C57 counterparts. Self-directed grooming in the presence of conspecific, was lower among vehicle treated, BTBR individuals relative to C57 mice. In the marble burying test, memantine treated BTBR mice buried fewer marbles compared to their vehicle treated counterparts. MRS data captured the model phenotype for BTBR mice that displayed higher levels of glutamine, glutamate + glutamine, glucose, phosphocreatine, creatine + phosphocreatine but lower lactate levels compared to C57 individuals. Among BTBR mice, positive control memantine attenuated glucose levels, caused GABA to decrease, further reduced the lactate levels, and increased glutamate + glutamine levels, relative to the vehicle treatment. Altogether, the BTBR mice expressed deficit in short-term spatial memory, increased self-grooming and altered behavior in social contexts compared to C57 mice. In addition, striatal MRS showed alterations in several metabolites. Behavioral phenotypes observed in BTBR mice capture a subset of the key deficits of ASD and can prove to be a useful model for identification of therapeutic interventions.

Disclosures: **U. Datta:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **T. Heikkinen:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **T. Bragge:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **R. de Feo:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **M. Dudek:** A. Employment/Salary (full or part-time):; Charles River Discovery Services. **K. McCullough:** A. Employment/Salary (full or part-time):; Jazz Pharma Inc. **P. Pine:** A. Employment/Salary (full or part-time):; Jazz Pharma.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.18/B24

Topic: A.07. Developmental Disorders

Support: NIH Grant: R03MH127401

Title: Deletion of SHANK3 gene leads to alterations in the morphology of astrocytes

Authors: *S. SUBA, D. BALLINAS, A. MCDONALD, T. DEEMYAD;
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Abstract: Synaptic connections in the brain consist of the presynaptic axon, the postsynaptic dendrite and the ensheathing astrocytic process. Astrocytes are morphologically complex, non-neuronal cells that play critical roles in synapse assembly, maturation and function. Many autism risk genes encode proteins that play critical roles in regulating the formation, maturation and function of synaptic connections in the brain, yet the underlying molecular mechanisms of autism are poorly understood. SH3 and multiple ankyrin repeat domains 3 (SHANK3) encodes different isoforms, including Shank3 deltac and Shank3b that stand as a prominent candidate in autism spectrum disorder. RNA sequencing of mouse and human brains revealed expression of SHANK3 gene in both neurons and astrocytes. Previous studies have shown that the loss of the Shank3 deltac isoform does not affect the size of astrocyte domains or cell body size in the hippocampus. However, the impact of eliminating the Shank3b isoform on astrocyte maturation, particularly within the cortical circuit, has not been clearly understood. Here, using electron microscopy and immunohistological assays we identified the developmental trajectory of astrocytes in auditory and somatosensory cortices of Shank3b KO mice. Our preliminary data obtained from Shank3b KO mice indicates a notable increase in the cell body density of astrocytes, particularly in layers 4 and 5 of the auditory and somatosensory cortices. These findings are observed both in adult mice as well as during the critical period of development. Furthermore, the sholl analysis conducted on the astrocytes reveals that the maximum increase in distal processes, leaflets, occurs at a distance of 200 nm from the soma. This indicates that the structural complexity of astrocytes and their perisynaptic territories, as reflected by the number of processes intersecting, is significantly altered in the absence of the Shank3b isoform. Taken together, these findings suggest that the elimination of the Shank3b isoform may indeed have an impact on the maturation of astrocytes within the cortical circuit, specifically in the auditory and somatosensory cortices.

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.19/B25

Topic: A.07. Developmental Disorders

Title: The effect of sulforaphane on autism spectrum disorder behaviors in BTBR mice

Authors: *S. RIEBESELL, N. TOUMANIOS, E. CRAIG, M. SCHMID, R. FREEDMAN, M. POMPY, C. CULLIGAN, C. MCGEARY, L. A. GABEL;
Lafayette Col., Easton, PA

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by restrictive behaviors and social deficits. BTBR T + Itpr3tf/J (BTBR) mice exhibit traits, such as poor social interaction and repetitive behaviors, with face validity to the diagnostic criteria for autism. At the cellular level, ASD is believed to be associated with oxidative stress, which leads to inflammation. Sulforaphane (SFN), a chemical derived from cruciferous vegetables, has been shown to have neuroprotective effects based on its antioxidant and anti-inflammatory properties. The purpose of the current study was to determine the effects of SFN on core symptoms of ASD and comorbidities, such as anxiety, hyperactivity, and impaired memory, in BTBR mice. We found that in the marble-burying task, BTBR mice buried significantly more marbles compared to controls (C57BL/6 [Bl6]), revealing a repetitive behavior phenotype of the BTBR strain, which was attenuated by self-administration of 50 mg/kg of SFN. Additionally, BTBR mice exhibited increased hyperactivity on the Y-maze based on a significant increase in the total number of entries compared to the Bl6 mice, which was ameliorated with SFN treatment. Lastly, SFN treatment increased social interaction in BTBR mice on the three-chamber task but decreased sociability for the Bl6 strain. However, BTBR mice treated with vehicle did not significantly differ from Bl6 mice suggesting they did not exhibit a sociability deficit, contrary to prior findings. We investigated the effect of SFN treatment on autistic-like behaviors and comorbidities in BTBR mice. Our results provide support for the efficacy of SFN treatment on repetitive behaviors and hyperactivity, but it is unclear whether SFN treatment will improve sociability based on the results from this study. BTBR mice did not exhibit impaired sociability on the three-chamber task, however, SFN treatment increased sociability in BTBR mice while decreasing sociability in Bl6 mice. Future studies will need to examine additional measures of sociability to confirm these findings, however, it is possible that BTBR mice may exhibit some, but not all, autistic-like behaviors to make it a suitable model of ASD.

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Poster

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Program #/Poster #: PSTR248.20/B26

Topic: A.07. Developmental Disorders

Support: NIH Grant 1R37NS114516-01A1

Title: Developmental Trajectory and Mechanisms of Genotype- and Sex-Dependent Differences in Auditory Sensitivity and Temporal Processing in a PTEN-deletion model of ASD

Authors: *K. CROOM[1], J. A. RUMSCHLAG[2], M. A. ERICKSON[1], D. K. BINDER[1], K. M. HUBER[3], K. A. RAZAK[1];
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Abstract: The current study aims to identify the developmental trajectory and mechanisms of genotype- and sex-dependent differences in auditory sensitivity and temporal processing in the PTEN-deletion (phosphatase and tensin homolog missing on chromosome 10) mouse model of autism spectrum disorder (ASD). ASD is currently diagnosed in approximately 1 in 44 children in the US and encompasses a wide array of debilitating symptoms, including sensory deficits. Sensory deficits early in development may lead to the broader symptomology in adolescents and adults with ASD, including abnormal language development. Auditory temporal processing is crucial for speech recognition and language development and deficits are hypothesized to cause language impairments in ASD. The mechanisms underlying sensory deficits may show sex-dependency. PTEN has sex-dependent interactions through its regulation of estrogen receptor α (ERα) and is also an ASD-linked gene, providing the opportunity to test whether and how sex-differences in sensory processing abnormalities may arise during development in an ASD model. We recorded epidural electroencephalography (EEG) signals from the frontal (FC) and auditory (AC) cortex in developing and adult Nse-cre PTEN mice, which removes PTEN in specific cortical layers (layers III-V) and the dentate gyrus. Temporal processing is measured using a gap-in-noise-ASSR (auditory steady state response) stimulus paradigm. The experimental manipulation of gap duration and modulation depth in the syllabic range of speech allows us to measure cortical entrainment to rapid gaps in sounds. We quantified temporal processing using inter-trial phase clustering (ITPC) values that account for phase consistency across multiple trials. The results show sex differences in resting power distribution in young mice (p21). Female, but not male, PTEN KO mice have increased beta power. This abnormal power distribution remains throughout development in females. Both male and female PTEN KO mice show diminished ITPC in their gap-ASSR responses in the AC and FC compared to control mice at all ages tested. These deficits become more prominent in adult (p60) mice, with KO mice having increased absolute resting and sound evoked power but significantly decreased ITPC compared to controls. These data suggest that auditory temporal processing deficits in PTEN ASD model mice are present from an early age and may contribute to abnormal development of speech recognition and language function in ASD. Future studies will include targeted treatments to gain insight into underlying mechanisms, critical windows of treatment and potential treatments in PTEN model mice.

Disclosures: K. Croom: None. **J.A. Rumschlag:** None. **M.A. Erickson:** None. **D.K. Binder:** None. **K.M. Huber:** None. **K.A. Razak:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Program #/Poster #: PSTR248.21/B27

Topic: A.07. Developmental Disorders

Support: Fondecyt Grant 1231556

Title: Characterization of transglutaminase role in Drosophila melanogaster neurodevelopment and behaviour

Authors: *I. ALMONACID-TORRES, M. GONZÁLEZ-RAMÍREZ, P. GÓMEZ-FETT, C. OLIVA, M. ANDRÉS, J. M. CAMPUSANO;
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Abstract: Transglutaminase 2 (TG2), a member of the transglutaminase family, plays a keyrole in several disorders including cancer progression, celiac and cardiovasculardiseases, among other conditions. It has been also suggested that TG2contributes to several brain disorders including neurodegenerative diseases andCNS injury, due to its ability to crosslink proteins into insoluble aggregates.Although recent reports support that TG2 plays a role in neural development, thisis still under investigation. In the *Drosophila melanogaster* genome there is onlyone transglutaminase (TG) gene which might be responsible for all actionsplayed by this enzyme family in other animals. In this exploratory research wehave asked whether flies deficient in TG expression exhibit behavioralphenotypes which could be linked to CNS structural alterations.We studied behavioural phenotypes in flies globally deficient in TG expression -Tg^{d01144} and *Tg-CRIMIC* mutants- or bearing a neuron specific deficiency for theTG enzyme. Female and male flies at different ages (3-5 and 8-10 days aftereclosion) were studied.Our data show that TG homozygous mutant animals exhibit reduced lifespan ascompared to heterozygous and control flies. TG mutant animals exhibit impairedstartle-induced climbing behaviour, while they show reduced locomotion whenthey are allowed to freely-move in a behavioral arena alone. TG mutant animalsalso exhibit increased centrophobism, which reflects anxiety. Additionally, the TGmutant flies exhibit reduced interaction time with their peers, which suggestasocial behavior.These behavioral phenotypes are accompanied by modifications in fly brainanatomy, evidenced by structural changes in the mushroom bodies, an importantassociation area in the fly brain.In conclusion, our data support that TG is a relevant enzyme in brain formationand operation.Supported by Fondecyt 1231556 (JMC).

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Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

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Topic: A.07. Developmental Disorders

Support: Autism Speaks Postdoctoral Fellowship
DOD Grant W81XWH-22-1-0880
Barbara Zucker Emerging Scientist Award

Title: Prenatal exposure to neurotoxic antibody leads to sex dependent dysregulation of parvalbumin interneuron development and hippocampal network activity

Authors: *C. BAGNALL-MOREAU, B. SPIELMAN, J. STROHL, C. CRUZ, P. HUERTA, L. BRIMBERG;
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Abstract: Autism Spectrum Disorder (ASD) is a heterogenous group of neurodevelopmental disorders that is characterized by impairments in social interactions, communication, and the presence of stereotypic behaviors. ASD affects 1 in every 36 children in the United States and is four times more prevalent in boys than in girls. Both genetic and environmental factors converge on deficits in the GABAergic system, suggesting that inhibitory interneurons might be particularly susceptible and contribute to ASD pathophysiology. Several studies, including our own, have demonstrated that 10-20% of mothers of a child with ASD harbor brain-reactive antibodies (IgG). One target of these antibodies is Caspr2, a protein involved in neural development and synaptic transmission, and present in up to 40% of mothers with anti-brain antibodies and an ASD child. We have developed a model in which female mice are immunized with Caspr2 and harbor endogenous polyclonal anti-Caspr2 IgG throughout gestation. Male, but not female offspring, display ASD-like behaviors and exhibit brain abnormalities including a reduction in the GABAergic parvalbumin interneurons (PV) in the cortex and hippocampus. We did not observe changes in the total GABAergic, nor in somatostatin interneurons suggesting that exposure in utero to anti-Caspr2 IgG selectively affects PV interneurons. The reduction in PV interneurons in Anti-Caspr2 male mice cannot be explained by a reduction in progenitors or altered migration as number of proliferating cells in the medial ganglion eminence (MGE) and the number of migratory interneurons were similar between Control and Anti-Caspr2 mice. Single nucleus transcriptomics of hippocampal GABAergic interneurons revealed significant alterations in gene pathways that are associated with neural transmission and CNS development. Furthermore, immunofluorescent imaging of synaptic protein expression in these mice revealed a reduction of perisomatic inhibitory synapses onto CA1 pyramidal neurons. We next sought to understand how these deficits in PV interneurons might affect neural activity in the hippocampus. We implanted multi-electrodes in Anti-Caspr2 male mice targeted to the CA1 region and calculated relative power in the gamma band. Anti-Caspr2 male mice exhibited a significant increase in mid and high gamma oscillations compared to Control mice. Since PV interneurons contribute to hippocampal network synchrony, and dysregulation of these cells is a proposed mechanism underlying ASD; ongoing studies are focused on the trajectory of PV

interneuron development and the effect of exposure in utero to anti-Caspr2 IgG on the intrinsic physiology of PV interneurons.

Disclosures: C. Bagnall-Moreau: None. **B. Spielman:** None. **J. Strohl:** None. **C. Cruz:** None. **P. Huerta:** None. **L. Brimberg:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.23/B29

Topic: A.07. Developmental Disorders

Support: NIH Grant NS105000
Eagles Autism Foundation Pilot Grant
RWJF Grant 74260

Title: Characterizing the Impact of Developmental Cc2d1a Reduction as a Novel Mouse Model of ASD/ID

Authors: A. T. HELLER[1], A. BHATTACHARYA[1], S. S. RAUF[1], *M. MANZINI[2];
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Abstract: Intellectual disability (ID) and Autism Spectrum Disorder (ASD) are highly heterogenous neurodevelopmental disorders that are thought to affect early brain development. Previous research has identified *CC2D1A* loss of function (LOF) as a cause of 100% penetrant ID, and highly penetrant ASD. Existing mouse models of *Cc2d1a* LOF rely on the conditional knockout (cKO) of *Cc2d1a* within specific cell types after birth due to early postnatal lethality of global knockouts (KOs). But cKO models have limited translatability to patients with *CC2D1A* LOF due to conditional and postnatal removal of the gene.
Our lab generated a mouse line tagged with both the V5 and HA epitope tags to improve endogenous CC2D1A detection but found that the tags lead to protein degradation. Homozygous CC2D1A-V5-HA mice ($Cc2d1a^{V5\text{-}HA}$) bypass postnatal lethality with a ~86% reduction of CC2D1A but did not recapitulate any of the ASD/ID-like behavioral deficits seen in cKOs. To investigate this phenotypic expression threshold, we generated a mouse line with severe haploinsufficiency (~92% protein reduction) of *Cc2d1a* by breeding a *Cc2d1a* KO allele with $c2d1a^{V5\text{-}HA}$, to obtain $Cc2d1a^{-/V5\text{-}HA}$ compound heterozygous (compHET) mice. These mice are viable and show no gross motor or sensory deficits. Behavioral analysis on a pilot cohort of male and female *Cc2d1a* compHET mice suggests male-specific deficits in sociability, social novelty preference, and spatial memory. While male-specific deficits have been seen in *Cc2d1a* cKOs before, these compHET males show a trend toward more severe social and cognitive deficits. Immunoblot analysis on the hippocampus and cortex of these males suggests CREB activation deficits different from those seen in previous *Cc2d1a* cKO models. While previous research on cKOs has implicated the PKA/CREB pathway, compHET males did not show changes in PKA

activation or cAMP levels. Instead, compHET males had decreased ERK1/2 and CaMKII activation in the cortex as well as reductions in CaMKII activation in the hippocampus. This preliminary, but growing data, suggests this severe developmental reduction of *Cc2d1a* in the mouse has unique neuronal mechanisms driving the ASD/ID-like phenotypes. The investigation of this model can help us better understand some of the mechanisms driving ASD and ID in *CC2D1A* LOF patients.

Disclosures: **A.T. Heller:** None. **A. Bhattacharya:** None. **S.S. Rauf:** None. **M. Manzini:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.24/B30

Topic: A.07. Developmental Disorders

Support: Roy J. Carver Charitable Trust

Title: Gestational influenza A virus disrupts downstream maternal and fetal immune profiles in a dose- and time-dependent manner

Authors: *A. OTERO[1,2], R. GONZALEZ-RICON[1,2], I. CHALEN[1,3], A. ANTONSON[1,3]; [2]Neurosci. Program, [3]Animal Sci., [1]Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: Epidemiological studies link neurodevelopmental disorders (NDDs) with exposure to maternal viral infection in utero. The hypothesized mechanism governing this link comes from animal models that initiate maternal inflammation with a non-pathogenic viral mimic to induce an acute immune response. These studies indicate that maternal intestinal T helper 17 (T_H17) cells are activated to produce interleukin (IL)-17, and this pro-inflammatory cytokine is implicated as a major driver of fetal brain abnormalities. Priming of T_H17 cells is also observed following respiratory influenza A virus (IAV) infection; however, whether these T_H17 cells might be driving fetal brain abnormalities during gestational IAV infection has never been examined. We aim to determine how IAV infection during pregnancy impacts maternal intestinal immune cells and if IAV-mediated activation of these cells is sufficient to result in aberrant brain development. To test our hypothesis, we inoculated pregnant C57BL/6NTac mice on gestational day (GD)9.5 with H3N2 IAV strain X31. Maternal serum, lungs, and intestine, placentas and fetal brains were collected on GD11.5 and 16.5, two- and seven-days post inoculation (dpi) to evaluate peak innate and adaptive immunity, respectively. Pregnant dams received 10^4 $TCID_{50}$ X31 ($X31_{hi}$; n=12, n=10), 10^3 $TCID_{50}$ X31 ($X31_{mod}$; n=14, n=9), or a mock-inoculation with saline (control; n=13, n=10) across three identical replicates per end point. Lung histopathology scores, viral expression, and inflammatory genes were upregulated in a dose- and time-dependent manner. Respiratory IAV infection led to colonic shortening at both time points despite no detection of virus in the intestine. Morphological changes were accompanied by upregulation of

T_H17 cell gene markers in the intestine at the high viral titer only. This includes genes encoding RORγt and IL-6, indicating priming of naïve T cells into T_H17 cells. Flow cytometric analyses of intestinal T_H17 cells at 2 and 7 dpi revealed a complex dose-dependent phenotypic shift. Placental immune transcripts were altered in a dose-dependent manner, demonstrating possible sequestering of adaptive immune cells and recruitment of neutrophils at the maternal-fetal interface. Immunohistochemistry revealed no changes in fetal microglial colonization patterns or proliferative capacities at GD11.5. Ongoing studies will analyze the fetal brain at GD16.5. So far, our data show that a higher infectious dose of gestational IAV is necessary to induce downstream immune changes, confirming the use of live pathogens in NDD modeling to evaluate the complete immune response and improve translation to the clinic.

Disclosures: A. Otero: None. **R. Gonzalez-Ricon:** None. **I. Chalen:** None. **A. Antonson:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.25/B31

Topic: B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

Support: NIH Grant 1K22NS105922-01

Title: Perirhinal cortex dysfunction drives spatial learning deficits in the Scn2a mouse model of autism spectrum disorder

Authors: *R. E. KEITH[1], J. A. MEZA[2], M. W. ANTOINE[3];
[1]Section on Neural Circuits, Natl. Inst. on Alcohol Abuse and Alcoholism, Fairfax Station, VA;
[3]Section on Neural Circuits, [2]Natl. Inst. on Alcohol Abuse and Alcoholism, Bethesda, MD

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder which often results in cognitive deficits, including that of spatial learning. Over 100 genes increase susceptibility to developing ASD. One such gene, *SCN2A*, codes for the alpha subunit of voltage gated sodium channel $Na_v1.2$, a protein critical for action potential back propagation. Loss of function mutations in *SCN2A* are highly penetrant for ASD, with up to 50% of patients diagnosed. Yet, much remains unknown about which brain regions are impaired by *SCN2A* loss and how subsequent activity changes drive ASD-related behaviors. To address this knowledge gap, we assessed spatial learning and whole-brain activity in mice haploinsufficient for *Scn2a* (*Scn2a*$^{+/-}$) and tissue-specific *Scn2a*-conditional *floxed* (*Scn2a*$^{fx/+}$) mutants. Consistent with prior work, *Scn2a*$^{+/-}$ mice exhibited a spatial learning deficit. Whole-brain light-sheet imaging for cFos (a neural activity marker) in *Scn2a*$^{+/-}$;FosGFP mice revealed hypoactivity in 31 brain areas, which were enriched in cortical areas implicated in spatial learning. We thus used an *Emx1*^{Cre} driver to reduce *Scn2a* in excitatory pyramidal neurons of cortex and hippocampus, and this recapitulated the learning deficit and neural hypoactivity in 15 cortical areas. We hypothesized

these 15 regions act as a spatial learning network. By comparing the pattern of Cre recombination in Cre driver lines which restrict reductions in *Scn2a* to cortical layers and hippocampus to spatial learning, we excluded hippocampus and instead implicated perirhinal cortex as a potential causal node for the spatial learning deficit. As *Scn2a* loss may impair the neuronal depolarization needed for long-term potentiation (LTP), a correlate of learning, we measured theta-burst LTP in cortical and hippocampal specific conditional mutants for *Scn2a*. The presence of spatial deficits co-associated with LTP impairments in perirhinal cortex but not hippocampus. Further, by chemogenetically increasing depolarization in cortical pyramidal neurons of $Emx1^{Cre};Scn2^{+/-}$ mice, we normalized activity within the 15 cortical regions, restored perirhinal cortex LTP, and rescued learning. We implicated perirhinal cortex as crucial for spatial learning by selectively reducing *Scn2a* in perirhinal cortex, via stereotaxic injection of Cre virus, which impaired learning, and, vice versa, selectively increasing perirhinal cortex activity of $hM3Dq^{fx/+};Scn2a^{+/-}$ mice rescued spatial learning. This research identifies a critical locus in cases of *Scn2a* haploinsufficiency that may be targeted to improve learning deficits in ASD and, perhaps, other neurodevelopmental disorders.

Disclosures: R.E. Keith: None. **J.A. Meza:** None. **M.W. Antoine:** None.

Poster

PSTR248. Autism: From Genes to Behavior and Neural Function

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR248.26/B32

Topic: B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

Support: NIH Grant R01 MH110487
MSCF Post-doctoral Fellowship Award

Title: Tcf4 mutations cause dysregulation of the oligodendrocyte linage in a human model of autism spectrum disorder.

Authors: *A. ROMERO-MORALES[1,2], G. SHIM[1], S. SRIPATHY[1], S. STUMP[1], J. BOHLEN[1], B. J. MAHER[1,2,3];
[1]Lieber Inst. for Brain Develop., Baltimore, MD; [2]The Solomon H Snyder Dept. of Neurosci., [3]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Pitt-Hopkins Syndrome (PTHS) is a rare form of autism spectrum disorder (ASD) characterized by developmental delay, breathing abnormalities, seizures, lack of speech, and distinctive facial features. PTHS is caused by de novo mutations in TCF4, a key transcription factor that orchestrates multiple neurodevelopmental programs. Previous studies using PTHS mouse models showed dysregulation in the density and maturity of oligodendrocytes which resulted in myelination deficits, however, confirmation of these phenotypes in a human context is currently lacking. Here, we have studied a collection of induced pluripotent stem cells (iPSCs) from PTHS patients, which harbor various types of disease-causing mutations in TCF4 that result

in the expression of putative dominant-negative proteins or haploinsufficiency. To determine if patient-specific mutations in TCF4 result in dysregulation of the OL lineage we first differentiated iPSC using a two-dimensional oligodendrocyte differentiation protocol. We observed that PTHS patient cell lines show a reduction in the expression of mature oligodendrocytes genes, which is consistent with phenotypes observed in mouse models of PTHS. In addition, using a previously described three-dimensional differentiation protocol that generates human oligodendrocytes (hOLS), we observed a significant variation ($p=0.0103$ for Genotype interaction, two-way ANOVA) in the diameter hOLS derived from PTHS that appears specific to patients harboring mutations expected to result in TCF4 haploinsufficiency. Together, these results suggest that TCF4 is a critical regulator of OL development and therefore predicts myelination deficits as a potential pathophysiological mechanism underlying neurodevelopmental abnormalities in PTHS.

Disclosures: A. Romero-Morales: None. **G. Shim:** None. **S. Sripathy:** None. **S. Stump:** None. **J. Bohlen:** None. **B.J. Maher:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.01/B33

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Title: Differential plasticity in nucelus accumbens group 1 metabotropic glutamate receptors following limited- versus extended-access to cocaine self-administration

Authors: *B. R. FINE-RAQUET, L. METKO, M. BERGMANN, T. MAXIM, M. B. GHASEMZADEH;
Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Repeated high-dose cocaine abuse results in drug addiction in humans demonstrating loss of control for drug use concurrent with gradual increase in drug intake, intense craving, and withdrawal symptoms. In preclinical studies, high-dose cocaine intake can be modeled by extended-access cocaine self-administration in rodents (LgA, 6hr daily). The persistent propensity to relapse during abstinence is often associated with drug-related cues and has been a significant barrier to the treatment of addiction. Addiction studies suggest that glutamatergic signaling has an important role in cocaine addiction, particularly in drug seeking and relapse. Hence, significant effort has been invested to harness glutamatergic mechanisms for treatment of cocaine addiction. However, this research has not yet resulted in an FDA-approved treatment. The goal of the present research project is to investigate the role of group 1 metabotropic mGlu1/5 receptors (mGluR1/5) in regulation of cocaine intake and seeking. Male Sprague-Dawley rats were trained to self-administer cocaine (FR1; 1.0 mg/kg/200µl/inf) during either 2hr (ShA) or 6hr sessions (LgA) for 14 days. Subsequently, animals remained in the home cage for 3, 10, or 60 days. Following abstinence period, rats were tested for cocaine seeking under

context-primed extinction condition after systemic administration of either saline or an mGluR1/5 antagonist [JNJ16259685 (0.015 mg/kg, sc) or MTEP (3 mg/kg, ip)]. Systemic blockade of mGluR5 during short abstinence periods (3 or 10 days) reduced drug-seeking only in ShA rats without affecting LgA animals, while mGluR1 blockade was effective in both treatment groups at both withdrawal times. However, systemic blockade of either receptor led to a significant reduction in drug-seeking after a long abstinence period (60 days) in both ShA and LgA treatment groups. While intracerebral infusion of MTEP (3 μg/side) after 10 days of abstinence into either NAcore or NAshell leads to a decrease in drug-seeking in ShA rats, inhibition of NAshell mGluR1 does not block drug seeking. Interestingly, inhibition of mGluR5 in NAcore or NAshell following 10 days of abstinence was not effective in reducing drug-seeking in LgA rats. Data suggest that high-level cocaine intake produces a transient intake-dependent plasticity in NA mGluR5, but not in mGluR1 function. Moreover, our data point to both NAcore and shell as anatomical substrates contributing to selective modulation of mGluR5 function in LgA rats. These observations suggest that systemic activation of mGluR5, during early abstinence period may ameliorate the persistent drug craving present during prolonged periods of abstinence.

Disclosures: **B.R. Fine-Raquet:** None. **L. Metko:** None. **M. Bergmann:** None. **T. Maxim:** None. **M.B. Ghasemzadeh:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.02/B34

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: The Uehara Memorial Foundation
Japan Society for the Promotion of Science Grant 22K15196

Title: An activity-dependent local transport regulation via local synthesis of kinesin superfamily proteins (KIFs) underlying cognitive flexibility

Authors: *S. IWATA[1,2], M. MORIKAWA[2], T. SASAKI[1], Y. TAKEI[1];
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Abstract: Multiple neuronal functions require decentralized processes including activity-dependent localized protein synthesis. However, how local protein synthesis drives the dendritic remodeling is still elusive. Kinesin superfamily proteins (KIFs) are microtubule-based motor proteins that transport various types of cargos to a specific area where they function, even to the distal neurites if necessary. This intracellular transport system is essential for neuronal morphogenesis, function, and survival. KIF17 and KIF5A are abundantly expressed in neurons and have been suggested to transport NMDAR and AMPAR in neuronal dendrites, respectively.

Calcium-calmodulin-dependent protein kinase II (CaMKII)-dependent phosphorylation of KIF17 triggered by NMDAR-mediated activity regulates its capacity for binding/release of NR2B-containing vesicles, and acute increase in intracellular Ca^{2+} through NMDAR regulates the speed of AMPAR transport. Thus, we hypothesized that KIF17 and KIF5A might be functionally regulated by NMDAR-mediated neuronal activity. Here, we show that KIF17 is rapidly degraded by the proteasome and subsequently synthesized at dendritic shafts in an NMDAR-mediated activity-dependent manner. Accompanied by the degradation of KIF17, its transport is temporarily dampened in dendrites. We also report that activity-dependent local KIF17 and KIF5A synthesis driven by its 3' untranslated region (3'UTR) occur at dendritic shafts, and the newly synthesized KIF17 moves along the dendrites. Furthermore, hippocampus-specific deletion of *Kif17* 3'UTR disrupts KIF17 synthesis induced by fear memory retrieval, leading to impairment in extinction of fear memory. These results suggest that the regulation of the transport by KIF17 and KIF5A is driven by the single dendrite-restricted mechanism including local protein synthesis that underlies cognitive flexibility. This model could help further understanding how a single dendrite serves as the computational unit for the memory process.

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Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.03/B35

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: ERC CoG 865634

Title: Ketamine induces direct presynaptic enhancement of glutamate release

Authors: *A. ESHRA[1], N. LIPSTEIN[2], S. HALLERMANN[3];
[1]Univ. of Leipzig, Leipzig, Germany; [2]Leibniz-Forschungsinstitut for Mol. Pharmacol., Berlin, Germany; [3]Univ. Leipzig, Leipzig, Germany

Abstract: Ketamine exerts rapid and sustained antidepressant effects via mechanisms involving sustained alteration of glutamatergic signaling, yet the immediate effects of ketamine on presynaptic function are poorly understood. Dissecting this effect is particularly difficult because of the ketamine-induced neuronal circuit potentiation which occurs via alteration of postsynaptic glutamate receptors. To unequivocally isolate the presynaptic mechanisms of ketamine and rule out potential neuronal network effects, we here used direct presynaptic recordings at a bona-fide cerebellar synapse in the intact brain tissue where the cell soma was removed. We performed 238 presynaptic recordings in 5 independent blinded experimental datasets and found that ketamine has a prominent direct effect on presynaptic release. We show that ketamine induced an enhancement of presynaptic release by approximately 30% within 30 minutes. The enhancement of release was sustained for at least 30 minutes after ketamine washout. Comparative

experiments with MK-801 revealed no effect on presynaptic function indicating that NMDA-receptors blockade in itself does not enhance presynaptic release. Further mechanistic analysis indicated that the ketamine-induced enhancement of presynaptic release is due to an increase in both calcium influx and the number of presynaptic release sites. Our results thus show that ketamine potentiates glutamate release via direct presynaptic mechanisms.

Disclosures: A. Eshra: None. **N. Lipstein:** None. **S. Hallermann:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.04/B36

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Title: Silica nanoparticles decrease glutamate uptake in blood-brain barrier components

Authors: *F. R. E. D. SANCHEZ;
Toxicology, Ctr. for research and advanced studies from national polytechnic institute, Mexico city, Mexico

Abstract: Silica nanoparticles (SiO_2-NPs) have been widely used in biomedical applications and directed to enter the circulatory system; however, little is known about the potential adverse effects of SiO_2-NPs exposure on the blood-brain barrier (BBB) transport systems that support the critical barrier function between the central nervous system (CNS) and the peripheral circulation. This study investigated whether SiO_2-NPs disrupt the transport systems expressed by BBB cell components. First, we evaluated the cytotoxic effect of SiO_2-NPs endothelial (HBEC) and astrocyte (U-87MG) cell lines. Transport kinetics was measured, and the exposure effect of SiO_2-NPs on glutamate transport activity was evaluated in both cell lines. Exposure of cell lines to different SiO_2-NPs concentrations (0.4, 4.8, 10 y 20 µg/ml) and times (3 and 6 hours) resulted in no changes in cell viability. We found that the radio-labeled D-aspartate ([^{3}H]-D-Asp) uptake is sodium-dependent, at least in part, and downregulated by its own substrate (glutamate). Furthermore, SiO_2-NPs exposure on endothelial and astrocytes decreases [^{3}H]-D-Asp uptake at different concentrations (2.4, 4.8, 6.4 y 10 µg/ml). Interestingly, a decrease in the transporter catalytic efficiency, probably linked to a decrease in the affinity of the transporter was detected upon SiO_2-NPs exposure. These results demonstrate that SiO_2-NPs could disrupt BBB function and can help to understand the effects of air pollution on the CNS.

Disclosures: F.R.E.D. Sanchez: None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.05/B37

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NINDS R01 NS113499
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NINDS NS100706
NINDS F99 NS134140-01

Title: Kir4.1 channels shape astrocyte membrane potential and modulate glutamate uptake: implications for traumatic brain injury

Authors: *J. GARCIA[1], M. ARMBRUSTER[1], C. DULLA[1], D. K. MULKEY[2], S. NASKAR[3]; [1]Tufts Univ. Grad. Program In Neurosci., Boston, MA; [2]Univ. Connecticut, Univ. of Connecticut Physiol. & Neurobio., Storrs Manfld, CT; [3]Tufts Univ. Sch. of Med., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Glutamate, the primary excitatory neurotransmitter in the central nervous system, is essential for normal brain function. In the healthy brain, once released from neurons, glutamate is transported into astrocytes by the excitatory amino acid transporters (EAATs) GLT-1 and GLAST. Previously, using iGluSnFr-based glutamate imaging and electrophysiology in the healthy adult mouse cortex, we have shown that glutamate uptake slowed up to threefold following bursts of neuronal activity. We suspect that this occurs because neuronal activity generates action potentials, causing focal increases in extracellular potassium ($[K^+]_e$). This increase in $[K^+]_e$ drives local astrocyte depolarization, causing voltage-dependent inhibition of EAATs and prolonging extracellular glutamate transients. We hypothesize that EAATs drive uptake while Kir4.1 shapes activity-dependent slowing of glutamate. In this study, I employed the controlled cortical impact (CCI) model of TBI in mice. TBI affects over 60 million people worldwide and multiple studies show that glutamate levels are increased in the human brain after TBI, as well as in animal models and in patients are associated with increased mortality. Three days after CCI I found significantly elevated glutamate decay time constants and increased peak glutamate response in acute cortical slices. This effect was decreased 7 and 14 days after injury. The slowing of glutamate uptake was largely similar in the healthy and injured brain for all time points. IHC and single-cell RNA sequencing data show significantly decreased levels of astrocyte-specific GLT1 and GLAST that return to sham levels 7 and 14 days after injury. Interesting Kir4.1 expression remains largely unchanged for all time points. Additionally, using a $Kir4.1^{fl/fl}$ mouse model and an astrocyte-specific Cre-virus I have conditionally and focally knocked out Kir4.1. Previously, using Genetically Encoded Voltage Indicators (GEVI), we reported report large, rapid, focal, and pathway-specific depolarizations in peripheral astrocyte processes (PAPs) during neuronal activity. We have shown blocking Kir4.1 using Ba^{2+} increases activity-induced PAP depolarization and overexpression of Kir4.1 decreases activity-induced PAP depolarization. I utilized GEVIs, to enable the measurement of V_m at PAPs. Conditional knockout of Kir4.1 resulted in a significant increase in GEVI $\Delta F/F_0$, suggesting that Kir4.1-medicated K^+ influx helps minimize activity-dependent PAP depolarization. We are currently expanding our work to include single-cell patch-clamp and glutamate imaging to further investigate the direct effect of potassium buffering on glutamate dynamics.

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Poster

PSTR249. Glutamate and Acetylcholine Transmission

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Program #/Poster #: PSTR249.06/B38

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Intramural Research Program

Title: Redox-dependent activation of protein kinase C and neurotransmitter transporter trafficking

Authors: *S. RADHAKRISHNAN[1], S. G. AMARA[2];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]NIMH, NIMH, Bethesda, MD

Abstract: Plasma membrane neurotransmitter transporters clear neurotransmitters from the extracellular space and play a key role in regulating neuronal signaling. The neuronal excitatory amino acid transporter 3, EAAT3, is essential for glutamate clearance and modulation of glutamatergic tone. EAAT3 also transports cysteine into the cell where it serves as a rate-limiting substrate for the synthesis of glutathione, a key neuronal antioxidant. EAAT3 mutations are associated with several neuropsychiatric disorders such as schizophrenia and obsessive-compulsive disorders that may be due to its role in glutamate or cysteine transport. The activity of plasma membrane transporters can be altered by changes in transport kinetics, expression levels and trafficking to and from the plasma membrane. Using surface biotinylation assays and radiolabeled glutamate uptake studies, we confirmed that activation of protein kinase C (PKC) can increase cell surface localization of EAAT3 in Neuro2A cells and mouse primary cortical neurons, as previously reported in other cell lines. Redox-triggered mechanisms can influence signaling through PKC by altering the catalytic properties or the subcellular compartmentalization of various PKC isoforms. This suggests a mechanism whereby EAAT3 trafficking could be modulated by cellular redox stress and PKC activation to increase cysteine import. We observed that oxidizing agents such as hydrogen peroxide can enhance PKC activation and surface expression of EAAT3 in both EAAT3-transfected Neuro2A cells and in primary cultures of mouse cortical neurons. To further understand the specific subcellular localization of this PKC activation, we targeted the genetically-encoded fluorescent PKC sensor, CKAR to lipid raft and non-raft membrane using a Lyn Kinase and KRAS targeting motif, respectively. The activation of PKC with hydrogen peroxide caused an increase in PKC activation at the non-raft membrane but did not cause a significant increase near the lipid raft. This PKC activation was reversed with the pre-application of a PKCθ selective inhibitor. We also observed that pre-application of a PKCθ selective inhibitor reduced a PMA-mediated increase in glutamate uptake in EAAT3-transfected Neuro2A cells. From previous research, we know that EAAT3 associates with non-raft membranes suggesting that this targeted PKC

activation could be relevant to understanding the redox mediated increase of EAAT3 at the membrane. Taken together our observations suggest specific subcellular localization for the redox mediated activation of EAAT3 trafficking to the membrane and the potential involvement of the PKCθ isoform in regulating EAAT3.

Disclosures: S. Radhakrishnan: None. **S.G. Amara:** None.

Poster

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Title: Deletion of xCT exclusively on immune cells is not sufficient to obtain preservation of hippocampus-dependent memory

Authors: *L. DE PAUW[1], J. O. ADEYEMI[1], O. LARA[1], P. JANSSEN[1], L. MACKENS[1], A. VILLERS[2], H. SATO[3], M. DE RIDDER[4], G. ATES[1], L. RIS[2], A. MASSIE[1];
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Abstract: The cystine/glutamate antiporter system x_c^-, is expressed on glial cells of the central nervous system (CNS) as well as cells related to the immune system. Imported cystine serves as building block for glutathione, while exported glutamate can modulate glutamatergic neurotransmission and alter the excitotoxic threshold in the CNS. We recently showed that xCT deletion (specific subunit of system x_c^-) results in lifespan extension as well as protection against age-related hippocampal dysfunction, memory loss and exacerbated inflammatory responses. Given the influence of blood-borne factors on brain aging, and given that exposure to low-grade peripheral inflammation seems to be sufficient to induce impaired neurogenesis and cognitive function, we hypothesized that the absence of system x_c^- on the cells of the peripheral immune system alone might be sufficient to obtain the beneficial effects seen in $xCT^{-/-}$ mice.
We generated chimeric mice in which system x_c^- is exclusively present on or absent from the peripheral immune cells, by performing bone marrow transplantations (BMT). Adult (8w) male Ly5.1 mice and $xCT^{-/-}$ mice underwent BMT with either xCT wild type ($xCT^{+/+}$) or $xCT^{-/-}$ donor BM from 14-16w old male mice. At 6 and 14 months post-BMT, mice were tested in a battery of

behavioral tests to evaluate locomotor function, memory, anxiety- and depressive-like behavior, after which mice were sacrificed to evaluate neuroinflammation and -degeneration. Hippocampal neurotransmission was analyzed through slice electrophysiology experiments at 15 months post-BMT.
Although we did see aging effects on the behavior of the mice for both recipient groups, the genotype of BM cells did not induce major changes in hippocampal neurotransmission or spatial memory in both recipient groups. Moreover, aging induced an expected increase in number of microglia and cortical thinning in all groups, without any striking differences induced by the lack of xCT on immune cells. It should be noted, however, that the performance of irradiated $xCT^{-/-}$ mice, independent of the BM genotype, is overall poor compared to Ly5.1 recipient mice as well as to our previous observations in $xCT^{-/-}$ mice, suggesting an increased sensitivity for irradiation induced (brain) damage.
So far, we can conclude that the absence of xCT exclusively on the cells of the peripheral immune system is not sufficient to protect mice against age-related cognitive decline and/or neuroinflammation nor is the presence of xCT exclusively on immune cells sufficient to induce either of these characteristics.

Disclosures: **L. De Pauw:** None. **J.O. Adeyemi:** None. **O. Lara:** None. **P. Janssen:** None. **L. Mackens:** None. **A. Villers:** None. **H. Sato:** None. **M. De Ridder:** None. **G. Ates:** None. **L. Ris:** None. **A. Massie:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.08/B40

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: Kom Op Tegen Kanker ANI219
Strategic Research Program of the Vrije Universiteit Brussel SRP49
Scientific Fund Willy Gepts
Oncology Research Center of the Vrije Universiteit Brussel
FWO fellowship 11658ON
FWO fellowship 11C2719N
FWO fellowship 12B3223N

Title: Optimization and characterization of a bone marrow transplantation mouse model and its use to study the role of system x_c^- in LPS-induced neuroinflammation

Authors: *P. JANSSEN[1], L. DE PAUW[1], M. MAMBRETTI[1], O. LARA[1], J. WALCKIERS[1], L. MACKENS[1], I. ROOMAN[1], H. SATO[2], B. GUILLAUME[3], M. DE RIDDER[4], G. ATES[1], A. MASSIE[1];
[1]Vrije Univ. Brussel, Brussels, Belgium; [2]Niigata Univ., Niigata, Japan; [3]UCLouvain, Brussels, Belgium; [4]UZ Brussel, Brussels, Belgium

Abstract: System x_c^-, a cystine/glutamate antiporter with xCT as specific subunit, is mainly expressed in the brain and on cells of the immune system. xCT has been proposed as a promising target to reduce (neuro)inflammation but its specific function on immune cells remains unclear. To study the involvement of immune cell xCT in the protective effects against LPS-induced neurological dysfunction that we previously observed in $xCT^{-/-}$ mice, we first optimized a protocol to generate bone marrow (BM) chimeras. Using 2x550cGy total body irradiation (TBI), we obtained a robust and stable model reaching near complete BM replacement with maximal survival. Since long-term consequences of TBI and bone marrow transplantation (BMT) performed on healthy adult mice have been poorly studied, contrary to the consequences of radiation on the juvenile body and brain, we next characterized the effects of the procedure on the overall health and brain of C57BL/6 mice. We found a persistent decrease in weight along with long-term impact on locomotion after TBI/BMT. Although the TBI/BMT procedure did not lead to mood disturbances 2- or 16-months post BMT, long-term spatial memory of the irradiated mice was impaired. While altered memory function after irradiation has been linked to neurodegeneration and neuroinflammation, we did not observe this at the timepoints we investigated. Yet, higher levels of hippocampal IgG in aged BMT mice suggest an enhanced age-related increase in blood-brain barrier permeability, potentially contributing to the observed memory deficit. Thus, although overall health of the mice did not seem to be impacted by TBI and BMT, TBI-induced impairment of locomotion and spatial memory could bias the behavioral read-out obtained from mouse chimeras with different genetic backgrounds that might display altered susceptibility to radiation-induced damage. Finally, we injected lethally irradiated Ly5.1 mice with $xCT^{-/-}$ or $xCT^{+/+}$ BM cells with a sublethal dose of LPS (5mg/kg) and found that mice lacking xCT only on their immune cells already recovered from LPS-induced hypothermia within 24h, contrary to $xCT^{+/+}$ BMT mice. Moreover, preliminary findings show that neuroinflammation was slightly attenuated in $xCT^{-/-}$ BMT mice one week post LPS injection as observed in the expression of pro-inflammatory cytokines and microglia activation in the hippocampus. However, while some minor beneficial effects of lacking xCT on immune cells could be seen during the LPS challenge, it seems that targeting xCT in the brain is required to reach significant protection against (neuro)inflammation.

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Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.09/B41

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: FWO fellowship 11C2719N
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FWO fellowship 12B3223N

Scientific Fund Willy Gepts
Oncology Research Center
Strategic Research Program VUB SRP49
Kom op tegen Kanker ANI219

Title: Tackling pancreatic cancer from different angles: compartmentalized role of xCT in supporting tumor growth and inflammation-related comorbidities in mice

Authors: *O. LARA[1], P. JANSSEN[1], M. MAMBRETTI[1], L. DE PAUW[1], G. ATES[1], L. MACKENS[1], J. DE MUNCK[1], J. WALCKIERS[1], Z. PAN[1], P. BECKERS[2], E. ESPINET[3], H. SATO[4], M. DE RIDDER[5], D. L. MARKS[6], K. BARBÉ[1], J. AERTS[1], E. HERMANS[2], I. ROOMAN[1], A. MASSIE[1];
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Abstract: While targeting of xCT, the specific subunit of the cystine/glutamate antiporter system x_c^-, has been reported to have cytotoxic effects on tumor cells, most of the studies ignore the possible involvement of this antiporter in cancer-related (neurological) comorbidities. Cachexia, a metabolic disorder characterized by loss of muscle mass and anorexia, as well as depression are frequently associated with (pancreatic) cancer and are both related to peripheral and central (in hypothalamus and hippocampus, respectively) inflammation. As xCT is also present in the brain and on immune cells, thereby modulating glutamatergic neurotransmission, behavior and inflammatory responses, we studied the impact of genetic xCT deletion in a murine pancreatic cancer model, not only on tumor growth but also on (neuro)inflammation, cachexia and mood disturbances. We used male mice with genetic deletion of xCT ($xCT^{-/-}$) and wildtype $xCT^{+/+}$ littermates, as well as Ly5.1 males that were sublethally irradiated and transplanted with bone marrow (BM) originating from $xCT^{+/+}$ or $xCT^{-/-}$ mice. xCT knockout Panc02 cells -generated using CRISPR/Cas9- were injected intraperitoneally in mice. To assess cachexia, food intake and muscle mass were assessed. Anxiety-like behavior was analyzed using the open field test, and the tail suspension test and forced swim test were performed to assess depressive-like behavior. Tumor xCT deletion resulted in a significant reduction of tumor burden, while only targeting xCT in the host had reduced benefit. Yet, the latter was sufficient to attenuate the tumor-related increase in systemic inflammation and immunosuppressive regulatory T (Treg) cells. This effect was only partly mediated by xCT on the immune cells, as we could only observe a reduced Treg population -and not reduced inflammation or tumor growth- in BM chimeras with specific immune xCT deletion. Besides affecting peripheral inflammation, xCT deletion in the host or tumor differentially modulated neuroinflammation. Hypothalamic inflammation was reduced in mice grafted with xCT deficient tumors, in line with improved cachexia parameters, whereas hippocampal inflammation was slightly attenuated by xCT deletion in the host, and was accompanied by reduced anxiety- and depressive-like behavior in tumor-bearing $xCT^{-/-}$ mice compared to $xCT^{+/+}$ mice. Taken together, targeting xCT in pancreatic cancer has beneficial effects on systemic and central inflammation, leading to attenuated cancer-related comorbidities. Novel and specific xCT inhibitors will thus have added beneficial effects in the central nervous system, beyond direct growth inhibition of pancreatic tumors.

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Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

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Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

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Title: The new mechanisms to regulate L-glutamate transporters - the interaction of polyunsaturated fatty acids and Leucine 434

Authors: K. TAKAHASHI[1], L. CHEN[2], M. WU[2], M. SAYAMA[2], M. KATO-HAYASHI[3], T. IRIE[1], T. OHWADA[2], ***K. SATO**[1];
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Abstract: Astrocytic excitatory amino acid transporter 2 (EAAT2) playsa major role in removing the excitatory neurotransmitter L-glutamate (L-Glu)from synaptic clefts in the forebrain to prevent excitotoxicity.Polyunsaturated fatty acids such as docosahexaenoic acid (DHA, 22:6 n-3)enhance synaptic transmission, and their target molecules include EAATs. Here,we aimed to investigate the effect of DHA on EAAT2 and identify the key aminoacid for DHA/EAAT2 interaction by electrophysiological recording ofL-Glu-induced current in *Xenopus* oocytestransfected with EAATs, their chimeras, and single mutants. DHA transientlyincreased the amplitude of EAAT2, but tended to decrease that of EAAT1, anotherastrocytic EAAT. Single mutation of leucine (Leu) 434 to alanine (Ala)completely suppressed the augmentation by DHA, while mutation of EAAT1 Ala 435(corresponding to EAAT2 Leu434) to Leu changed the effect from suppression toaugmentation. Other polyunsaturated fatty acids (PUFAs) (docosapentaenoic acid,eicosapentaenoic acid, arachidonic acid, and a-linolenic acid) similarlyaugmented the EAAT2 current and suppressed the EAAT1 current. Finally, ourdocking analysis suggested the

most stable docking site is the lipid crevice ofEAAT2, in close proximity to the L-Glu and sodium binding sites, suggestingthat the DHA/Leu434 interaction might affect the elevator-like slide and/or theshapes of the other binding sites. Clustering of accessible conformations ofDHA in water indicated the probability of U-shaped DHA is highest, which wasconsistent with the structure suggested by the docking study. Collectively, ourresults highlight a key molecular detail in the DHA-induced regulation ofsynaptic transmission involving EAATs. Ref) Takahashi K, Chen L, Sayama M, Wu M, Kato Hayashi M,Irie T, Ohwada T, Sato K. Leucine 434 is essential for docosahexaenoicacid-induced augmentation of L-glutamate transporter current. J Biol Chem. 2023Jan;299(1):102793. doi: 10.1016/j.jbc.2022.102793. Epub 2022 Dec 9.

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Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.11/B43

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant RO1-NS094404

Title: Contribution of synaptic glutamate vs. spiking activity to cerebral vascular responses in awake mice

Authors: *J. PERETIN[1], A. VAZQUEZ[2];
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Abstract: The brain accounts for roughly 20% of bodily metabolic demands, with the majority being accounted for by neuronal energy consumption for processes such as synaptic transmission, which has been reported to be more metabolically demanding than spike generation. Energy substrates necessary for these processes are delivered by the vasculature, but the impact of synaptic and spiking activity on blood supply has not been fully characterized. Insight into this relationship may be relevant to understanding brain metabolism in both normal and diseased brain states. In this study, we investigated the role of synaptic and spiking activity on local vascular changes in awake mice using fluorescent markers for extracellular glutamate (n=7) and intracellular calcium (n=3), respectively. Simultaneous measurements of vascular changes were obtained using hemoglobin absorption or fluorescent tracers as vascular agents. Low- and high-resolution imaging experiments were conducted during whisker stimulation and ongoing resting state conditions. Under lower resolution wide-field imaging, whisker stimulation produced a mean increase of 0.25% in glutamate signal and 2.91% in neuronal calcium signal relative to baseline. Under high-resolution two-photon imaging, the mean increase in glutamate fluorescence was 5.67% and was 28.93% for neuronal calcium fluorescence. These fluorescent responses to a single whisker puff exhibited mean decay time constants of 26.8 ms for glutamate

and 36.9 ms for calcium by wide-field imaging, with similar results using two-photon microscopy. Robust vascular changes were observed for all experiments. To determine the contribution of synaptic and spiking activity on vascular changes, we used a linear convolution model to predict vascular changes from these neural events. Explained variance (R^2) analyses were performed, and it was determined that the glutamate signal tended to be a better predictor of the evoked hemodynamic response when compared to the calcium signal. These findings suggest that synaptic glutamate activity may be more correlated with and predictive of cerebral blood flow changes than spiking activity, which could have implications in many neurodegenerative diseases associated with synaptic or vascular dysfunction.

Disclosures: J. Peretin: None. **A. Vazquez:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.12/B44

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIMH Grant: MH120174
NIMH Grant: MH119185
Lifespan Brain Institute (LiBI)

Title: Clinical rTMS Therapy Differentially Modulates Glutamatergic Neurometabolites: A Meta-Analytic Synthesis of ^{1}HMRS Studies in Psychiatric Populations

Authors: *M. PECSOK[1], A. MORDY[2], M. CRISTANCHO[3], D. OATHES[3], D. R. ROALF[3]; [1]Neurosci. Grad. Group, Univ. of Pennsylvania Neurosci. Grad. Group; Perelman Sch. of Med., Philadelphia, PA; [2]Dept. of Psychiatry, Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA; [3]Dept. of Psychiatry, Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA

Abstract: Background: Repetitive transcranial magnetic stimulation (rTMS) alleviates symptoms of major depressive disorder (MDD) and other psychiatric disorders but the neurobiological mechanisms of its clinical efficacy remain to be fully determined. Growing evidence from proton magnetic resonance spectroscopy (^{1}HMRS) studies suggests that rTMS alters the balance of excitatory and inhibitory neurometabolites.
Methods: Eligible studies that quantified Glutamate (Glu), Glutamate/Glutamine (Glx), or GABA levels before and after administration of rTMS were sourced from PubMed, MEDLINE, PsychInfo, Google Scholar, and primary literature following PRISMA guidelines. Data were pooled using a random effects model, Cohen's d effect sizes were calculated, and moderators were assessed. It was hypothesized that rTMS would increase glutamatergic neurometabolite concentrations at the rTMS target (DLPFC) and downstream regions. **Results:** Within-subjects data from 229 cases encompassing 42 neurometabolite effects (k) were included. Real rTMS in

clinical responders (N=151; k=28 effects) increased glutamatergic neurometabolites (d=0.20 [95% CI:0.04,0.35], p=0.01). No change was seen clinical non-responders (N=54 participants; k=7; d=0.48 [95% CI:-0.44,0.34], p=0.81) or sham rTMS participants (N=25 participants; k=7; d=0.033[95% CI:-0.34,0.40], p=0.86). Glu was significantly increased in downstream regions after rTMS (k=8, d=0.29 [0.013,0.58], p=0.04). Effect size was associated with the number of rTMS pulses patients received (p=0.05). **Conclusions and Relevance:** Clinical rTMS is associated with a small, distributed, and dose-dependent increase in glutamatergic neurometabolites, suggesting that rTMS may improve psychiatric symptoms by inducing synaptic plasticity and altering neurometabolism. Future studies should explore target and downstream effects, investigate behavioral implications of neurometabolite changes, and leverage ultra-high field MRI techniques for improved spatial resolution.

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Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.13/B45

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: Studies were supported by the NINDS Intramural Research Program

Title: Transcriptomic signatures of basal forebrain cholinergic neurons across lifespan

Authors: *M. R. ANANTH, R. KIM, D. A. TALMAGE, L. W. ROLE;
NINDS/NIH, Bethesda, MD

Abstract: Basal forebrain cholinergic neurons (BFCNs) are distributed throughout the base of the forebrain and send widespread projections throughout the brain. These neurons have been found to be critical in coordinating neuronal activity to promote attention and facilitate learning. While previously regarded as a uniform cluster of cells, growing evidence supports the assertion that subsets of BFCNs uniquely participate in cognitive behaviors. In addition, we have found region-specific vulnerability across cholinergic axonal arbors, where some projections deteriorate far sooner and to a much greater degree than others. Several factors could contribute to this heterogeneity across BFCN subpopulations including birthdate, projection target and gene expression profiles. Understanding the factors underlying BFCN diversity is critical to understanding the role of acetylcholine in cognition and its vulnerability in cognitive decline. In these studies, we first asked if cholinergic neurons could be distinguished by unique gene expression profiles, and second, whether any functionally unique clusters were specifically vulnerable across lifespan. Given the sparsity of BFCNs throughout the basal forebrain, a detailed classification of this population has been challenging thus far. To overcome this, we used a genetic strategy where cholinergic nuclei were specifically labeled with a nuclear

membrane targeted GFP. Using FACS, we isolated nuclei from dissections of the full anterior to posterior extent of the basal forebrain and enriched for cholinergic nuclei based on GFP expression. Libraries were prepared using 10X Chromium technology and sequenced using the Illumina sequencing platform. Our preliminary dataset included over 30 thousand GFP-captured cells in young male and female mice. After standard QC, we filtered our results toward ChAT-expressing nuclei. We performed clustering analysis to reveal several distinct cholinergic neuron clusters, representing far more diversity across the basal forebrain than initially hypothesized. Identified clusters include those highly NGFR and LHX8 expressing with varying Zic4 expression (which denotes septal and non-septal lineages) and some unexpected populations with low NGFR expression. Using Seurat, we identified biomarkers for each of our isolated cholinergic neuron clusters. Ongoing analyses investigate the patterning of these clusters spatially across the basal forebrain and the selective vulnerability of these subpopulations with age.

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Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.14/B46

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: This work was supported by NINDS IRP to L Role

Title: Evaluation of the morpho-electrical properties of basal forebrain cholinergic projection neurons

Authors: *G. WATKINS, N. DESAI, L. JIANG, F. LUO, R. KIM, D. TALMAGE, L. ROLE; NIH/NINDS, Bethesda, MD

Abstract: Acetylcholine is essential for proper development and function of the mammalian brain. Cholinergic innervation is provided by projections of the basal forebrain cholinergic neurons (BFCNs), which send axons to diverse structures throughout the brain. BFCNs are often subdivided into anatomically defined populations. Those located in the medial septum and the vertical limb of the diagonal band of Broca (MS/vDB) send projections to several target regions essential for learning and memory such as the hippocampal/subicular complex and the entorhinal cortex. Characterizing the role of MS/vDB cholinergic projections to the ventral subiculum is of particular interest, as it is one of the primary outputs of the hippocampus. Although disruption of normal cholinergic activity to both the hippocampus and the subiculum has been shown to contribute to learning and memory deficits, less is known about the properties of the MS/vDB cholinergic neurons themselves, or how they may differ from other BFCNs. To address this question, whole-cell recordings of ~30 cholinergic MS/vDB neurons were made from acute slices of adult mice in order to measure cell-intrinsic electrical properties. Following recording,

tissue was fixed so that neurons could be relocalized and reconstructed to measure morphological features. Electrical and morphological properties were then analyzed by UMAP and compared to data from cholinergic neurons in the nucleus basalis/substantia innominata (NBM/Si) and ventral pallidum (VP). We found that BFCNs from the three anatomical subregions separate into non-homogenous populations based on their basic properties; furthermore, within each nucleus, the projection target did not seem to correlate with any specific properties. Despite the differences in target, cholinergic neurons in MS/vDB share many electrical properties with those in NBM/Si, although the AP kinetics of MS/vDB neurons are slightly slower. When compared with cholinergic neurons in VP, which share many targets with those in NBM/Si, MS/DB cholinergic neurons have a longer AP latency, higher AP threshold, and a lower maximum firing rate.

Disclosures: G. Watkins: None. **N. Desai:** None. **L. Jiang:** None. **F. Luo:** None. **R. Kim:** None. **D. Talmage:** None. **L. Role:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.15/B47

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NINDS IRP

Title: Comparative physiology and morphology of BLA projecting cholinergic neurons in mouse and macaque

Authors: *F. LUO, N. DESAI, L. JIANG, G. WATKINS, L. BAI, R. KIM, D. TALMAGE, L. ROLE;
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Abstract: Cholinergic projection neurons in the basal forebrain (BF) are essential to learning and memory. BF cholinergic projection neurons (BFCN) are organized along the rostro-caudal axis of the adult mammalian forebrain, and include the medial septum, diagonal band (vertical and horizontal limbs), the substantia innominata, ventral pallidum (VP/Si_a), and nucleus basalis of Meynert (NBM/Si_p). These cholinergic projection neurons participate in an array of cognitive functions through the action of acetylcholine released at pre and post synaptic sites within multiple cortical and subcortical regions. Recent studies indicate that key determinants of BFCN fate include birth order and location, i.e., early-born cholinergic neurons are more caudally located, in contrast to later born rostral BFCNs *(see Ananth et al. Nat. Rev. Neurosci, 2023*). Despite temporal and spatial differences in origin, both VP and NBM/Si_p cholinergic fibers densely innervate the basal lateral amygdala (BLA). NBM/Si_p cholinergic inputs to the BLA are thought to be engaged in the acquisition and retention of emotional memories. The VP/Si_a cholinergic projection to BLA differentiates innate positive from negative valence stimuli. We

have conducted comparative studies of cholinergic neurons along the rostro-caudal extent of the BF in mouse and macaque. First we asked whether morphological and physiological profiles of mouse BFCNs correlate with A-P location (~birthdate) and/or their projection targets, comparing BLA projecting VP vs. NBM/Si_p neurons. Using retro-bead labeling of cholinergic projection neurons to the BLA we assessed 19 parameters by patch clamp recording. Biocytin injection was followed by relocalization, IHC confirmation and comparison of the electrophysiological and morphological profile of ~60 VP and NBM/SI cholinergic neurons, the majority of which shared the common projection to the BLA. To our surprise the most robust differences of electrophysiological and morphological features were found by comparing BLA projecting VP vs. BLA projecting NBM/Si_p neurons (i.e. independent of target). In a parallel study of the BLA projecting NBM cholinergic neurons from macaque, we found significant differences in most of the 19 physiological parameters tested compared with mouse. Sorting by bregma, dimensionless clustering analysis may suggest some AP-related features of the electrophysiology; comparison of monkey vs mouse somatodendritic morphology is underway. Ongoing work extends the mouse macaque comparison to other BLA projecting BFCNs and to include cortical targets. (Approved by NIH/NINDS ACUC; supported by NINDS IRP)

Disclosures: F. Luo: None. **N. Desai:** None. **L. Jiang:** None. **G. Watkins:** None. **L. Bai:** None. **R. Kim:** None. **D. Talmage:** None. **L. Role:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.16/B48

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIMH IRP NIH HHS 002887-15

Title: Disruption of cholinergic fibers of passage to the prefrontal cortex by aspiration removals of orbitofrontal cortex in rhesus macaques

Authors: *A. MOHANTY, B. E. HINES, M. A. G. ELDRIDGE, E. A. MURRAY; Neuropsychology, NIH, Natl. Inst. of Mental Hlth. (NIMH), Washington, MD

Abstract: Disruption of cholinergic fibers of passage to the prefrontal cortex by aspiration removals of orbitofrontal cortex in rhesus macaques Authors: A. Mohanty, B. E. Hines, M. A. G. Eldridge, E. A. Murray
Abstract The study of anthropoid nonhuman primates has provided valuable insights into frontal cortex function in humans, as these primates share similar frontal anatomical subdivisions. Causal manipulation studies have been instrumental in advancing our understanding of this area. One puzzling finding is that macaques with bilateral damage to the orbitofrontal cortex (OFC) made by aspiration, which directly removes the cortex, exhibit a different set of behavioral impairments than macaques with excitotoxic lesions of the same region. Specifically, rhesus

monkeys with bilateral aspiration removals of OFC are impaired on tests of cognitive flexibility and emotion regulation, whereas those with bilateral excitotoxic lesions of OFC are not (Rudebeck et al., *Nat. Neurosci.*, 2013). This discrepancy is attributed to the inadvertent disruption of fibers of passage by aspiration lesions but not by excitotoxic lesions. The underlying question is: Which fibers of passage are responsible for impairments in cognitive flexibility and emotion regulation when compromised? One candidate is the cholinergic fibers, originating in the nucleus basalis magnocellularis (NBM) and passing nearby or through OFC on their way to other frontal cortex regions (Kitt et al., *Brain Res*. 1987). To investigate this possibility, unilateral aspiration lesions were performed in the OFC of three rhesus monkeys, and the cholinergic innervation, as measured by AChE expression, of the anterior cingulate cortex (ACC) was compared between hemispheres with and without OFC. The assessment revealed diminished AChE expression in the ACC of hemispheres with OFC lesions, particularly in layers I and III/V. This disparity was more pronounced in the rostral ACC and less so in the more caudal regions. No difference was observed in cholinergic staining in the striatum, which receives cholinergic innervation from local interneurons. These findings suggest that aspiration lesions of the OFC disrupt cholinergic fibers of passage, potentially explaining the significant impairments in cognitive flexibility and emotion regulation observed in comparison to excitotoxic lesions. Further research is necessary to demonstrate a causal relationship between the interruption of cholinergic innervation in the frontal cortex and its effects on behavior.

Disclosures: A. Mohanty: None. **B.E. Hines:** None. **M.A.G. Eldridge:** None. **E.A. Murray:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.17/B49

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH/NINDS R01 NS069861
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NJCBIR CBIR16IRG017
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AES 957615

Title: Differential cholinergic modulations of dentate semilunar granule cell and granule cell excitability and synaptic inhibition

Authors: *A. HUANG[1], M. AFRASIABI[2], B. SWIETEK[3], V. SANTHAKUMAR[4];
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Abstract: The dentate gyrus (DG) is a sparsely firing region of the hippocampus critical for processing and formation of episodic memory. Recent studies have characterized two classes of DG projection neurons, granule cell (GC) and semilunar granule cell (SGC) which differ in morphology, location, and intrinsic physiology. As information about the preferential role of SGCs in memory engrams and synaptic physiology emerges, it remains unknown whether memory related neuromodulators such as acetylcholine (ACh) differentially impact GCs and SGCs physiology. Here we conducted whole-cell recordings from GCs and SGCs in hippocampal slices from male and female Wistar rats (P28-41) to examine cholinergic modulation of intrinsic physiology and synaptic inhibition. In both GCs and SGCs, the muscarinic ACh receptors (mAChRs) agonist, oxotremorine (oxo-M, 10μM), increased firing frequency in response to current below 160pA and decreased firing at current injections over 200pA. The mAChR dependent increase in firing was coupled to depolarizing plateau potentials (DPP) during current injections at rheobase, while decline in firing at high current injections resulted from depolarization block. Although mAChR agonist caused persistent firing and lowered action potential threshold in both cell types, it elicited greater increase in firing in SGCs than in GCs. Blocking transient receptor potential canonical isoforms 4/5 (TRPC4/5) channels, known to be activated downstream of mAChRs in GCs, with the selective antagonist M084 (10μM) did not alter firing frequency or action potential threshold in either cell type. However, preapplication of TRPC4/5 antagonist prevented the mAChR mediated reduction in action potential threshold without preventing DPP in both GCs and SGCs. These findings indicate that cholinergic regulation of DPP and action potential threshold likely involve distinct molecular mechanisms. Since SGCs and GCs differ in inhibitory inputs and interneurons show cell type specific cholinergic modulation, we next examined the effect of carbachol (CBC, 10 μM), a nonselective cholinergic agonist on synaptic inhibition onto GCs and SGCs. Although CBC reduced the amplitude of afferent evoked inhibitory synaptic currents in both cell types, it selectively reduced both frequency and amplitude of spontaneous inhibitory synaptic events in GCs but not SGCs. Together these studies demonstrate that cholinergic agonists preferentially enhance SGC excitability and impair GC inhibition which could contribute to the preferential recruitment of SGCs during memory formation.

Disclosures: **A. Huang:** None. **M. Afrasiabi:** None. **B. Swietek:** None. **V. Santhakumar:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.18/B50

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: This work was supported by funds from the NINDS IRP

Title: The septal-hippocampal cholinergic pathway in cue-conditioned threat learning

Authors: *C. ZHONG, N. S. DESAI, D. A. TALMAGE, L. W. ROLE;
NIH/NINDS, Bethesda, MD

Abstract: The cholinergic fibers of the medial septum/diagonal band of Broca (MS/DB) project to the hippocampal formation. Previous studies indicated that MS/DB cholinergic inputs to the ventral hippocampus (vHipp) are engaged in auditory cued fear memory but the precise spatial and temporal profile of acetylcholine (ACh) release and signaling remains unclear. To define specific roles for cholinergic regulation of vHipp mediated cue-conditioned threat learning, we have combined imaging of a genetically encoded calcium indicator (GCaMP, axonGCaMP) and an ACh sensor (Red-GRAB$_{ACh1.7}$), with transcriptional activity markers. Mice went through a classic auditory cue-conditioned fear training and recall paradigm (tone paired to shock and then recall to tone alone). Following different aspects of this paradigm the animal was sacrificed and we imaged cholinergic neurons within acute MS/DB slices or cholinergic projections within the vHipp. With GCaMP6f expressed specifically in cholinergic neurons in Chat-Cre mice, and a tTA-dependent activity labeling system (Robust Activity Marker, or RAM) to label neurons activated during the training session, we found: 1) increased number of RAM labeled cholinergic neurons after cue conditioned fear training; 2) a transient (up to 5 hours post training) increase in Ca^{2+} dynamics, measured as amplitude and frequency of Ca^{2+} oscillations, in RAM labeled cholinergic neurons; 3) 24 hours after training, Ca^{2+} dynamics were significantly enhanced in RAM labeled cholinergic neurons following tone alone (recall) presentation, as compared to RAM labeled cholinergic neurons without tone recall or in untrained mice in response to tone alone. Further studies examine the spatial and temporal profile of septal-hippocampal cholinergic transmission in vHipp using axonGCaMP6s (MS/DB projections) and ACh sensor. Opto-stimulation of cholinergic axons leads to increase of cholinergic axonal Ca^{2+} activity and elicits ACh release in vHipp. Ongoing studies examine the precise frequency and amplitude dependence of optogenetic stimulation on the response kinetics of cholinergic axonal activity and ACh release in vHipp.

Disclosures: C. Zhong: None. **N.S. Desai:** None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.19/B51

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NSF Grant #: 2131750

Title: Effects of Vesicular acetylcholine transporter overexpression on synaptic activity in Drosophila melanogaster

Authors: *K. ROSIKON[1], H. O. LAWAL[2], B. CHURCH[1];
[2]Biol., [1]Delaware State Univ., Dover, DE

Abstract: Impairment in cholinergic neurotransmission is associated with normal and pathological aging, making cholinergic release a subject of high interest. However, the precise role of changes in central acetylcholine release in mediating behaviors that range from locomotion to cognition has not been fully elucidated. The vesicular acetylcholine transporter (VAChT) is present in many species, including worms, flies, and humans, and is responsible for the packaging of acetylcholine for exocytotic release. Although there is a plethora of knowledge about the molecular machinery that regulates ACh, the exact manner in which VAChT, an essential component of ACh regulation, alters ACh-linked neuronal function remains a subject of active investigation. Here, we use the overexpression of VAChT as a tool to increase the amount of ACh released into the synaptic cleft. And we are measuring the effect of that altered state on synaptic activity using two key behavioral circuits, locomotion and cognition. We report that increased levels of VAChT do not affect locomotion in young flies but do so with age. Moreover, VAChT overexpression leads to a deficit in immediate recall, an important measure of cognitive capability in Drosophila. We also show that a vast increase in VAChT expression leads to an accumulation of the protein in synaptic vesicles and at the plasma membrane. We present an analysis of the effects of different levels of overexpression of VAChT on synaptic activity to ascertain whether those effects are dependent on the degree of VAChT overexpression. Taken together, these data provide further evidence for a role of central cholinergic release in the mediation of key neuronal functions and uncover insights into mechanisms that regulate acetylcholine exocytosis from neurons in the central nervous system.

Disclosures: K. Rosikon: None. **H.O. Lawal:** None. **B. Church:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.20/B52

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NSF Grant Proposal No. 2131750 (Lawal, PI)

Title: Effects of changes in vesicular acetylcholine transporter expression on the regulation of cholinergic pathway components

Authors: R. NEMAT, *H. LAWAL;
Delaware State Univ., Dover, DE

Abstract: Effects of changes in vesicular acetylcholine transporter expression on the regulation ofcholinergic pathway components Rohina Nemat and Hakeem O. LawalDelaware Center for Neuroscience Research, Department of Biological Sciences, Delaware StateUniversity, Dover DelawareCentral cholinergic neurotransmission is essential for the regulation of cognition and other acetylcholine-linked behaviors. Consequently, alterations in neuronal cholinergic signaling lead to an impairment inlearning and memory, although the

mechanism through which this deficit occurs is still not fully understood.The vesicular acetylcholine transporter (VAChT) mediates the packaging and transport of acetylcholine(ACh) for exocytotic release. And while much is known about the molecular machinery that regulates ACh,the precise manner in which VAChT, an essential component of ACh regulation, alters ACh-linked neuronalfunction remains a subject of active investigation. Here, we use the overexpression of VAChT (using aconstruct that we have reported on previously) as a tool to increase the amount of ACh released into thesynaptic cleft. And we are measuring the effect of that altered state on synaptic activity using a biochemicalapproach. We have optimized an assay that allows us to reliably measure cholinergic pathway componentsACh and choline from as little as ten *Drosophila* heads. Using this assay, we report the surprising data thatwhile VAChT overexpression does not increase total head ACh levels, there is an increase in choline levels,suggesting that there are homeostatic consequences for changes in VAChT expression. We also presentpreliminary findings from similar experiments with *Vacht* mutants that have reduced transporter expression.Taken together, these data provide further insight into the severe consequences that follow a disruption inVAChT expression and form a basis for more detailed optical and electrophysiological studies aimed atdissecting in cholinergic function neural circuits.

Disclosures: R. Nemat: None. **H. Lawal:** None.

Poster

PSTR249. Glutamate and Acetylcholine Transmission

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR249.21/B53

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: European Union ERC, Cortical Coupling, 101055340

Title: Interactions between metabotropic acetylcholine and glutamate receptors for the enhancement of dendro-somatic coupling of cortical pyramidal tract neurons

Authors: *A. BRONEC[1], M. SUZUKI[2], T. A. ZOLNIK[3], M. E. LARKUM[1];
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Abstract: In the somato-sensory cortex, the distal apical dendrites of cortical layer 5 pyramidal neurons (L5p) receive feedback inputs from higher-order cortical and thalamic regions, which convey important information related to reward, memory, and behavioral context. The impact of these feedback inputs on the somatic activity of these neurons depends on the dendro-somatic coupling, which represents how effectively dendritic depolarization propagates toward the soma and evoke somatic action potentials (APs). A previous in vivo study revealed that general anesthesia suppresses the dendro-somatic coupling of these neurons. Additionally, metabotropic receptors for acetylcholine (mAChRs) and glutamate (mGluRs) were found to significantly

influence this coupling, but the underlying mechanisms and potential receptor interactions remain unclear. To address these questions, we used whole-cell recording, cell-type-specific expression of optogenetic actuator, and pharmacological application of metabotropic receptor agonists. We generated a mouse model by crossing the Sim1-Cre KJ18 transgenic mouse line with the Rosa26-ChR2 reporter line Ai32 to selectively express channelrhodopsin2 (ChR2) in the pyramidal tract (PT) neurons of L5p. Optogenetic stimulation using blue light was specifically applied to the distal apical dendrites. We used carbachol for mAChRs and (S)-3,5-DHPG for mGluRs to manipulate each type of metabotropic receptorOur preliminary findings from 8 PT neurons obtained from 7 mice showed that bath applications of 3 μM carbachol enhanced dendro-somatic coupling. Optogenetic stimulation of distal tuft dendrites evoked an increase in somatic activity in the presence of carbachol (n=6/8 neurons with an average increase of 43.48%) which supports previous in vivo investigations. Simultaneous application of DHPG (0.75 μM) and carbachol (3 μM) elicited more APs compared to carbachol alone (n=6/8 neurons with an average increase of 23.66%), suggesting potential interactions between the two types of metabotropic receptors. Further data collection and analysis, as well as investigation into downstream mechanisms such as IP3-mediated intracellular calcium release, will be conducted to better understand these interactions.

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Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.01/B54

Topic: D.01. Somatosensation

Support: NIH grant NS055159
NCI-CCSG P30CA072720-5922
NIH predoctoral fellowship F31NS125940

Title: Inhibition of the TRPM3 ion channel is involved in opioid-induced itch

Authors: N. KIM[1], Y. YUDIN[2], C. BURTON[1], H. HU[1], Z. KISS[1], S. SU[1], ***T. ROHACS**[3]; [2]Rutgers New Jersey Med. Sch., [1]Rutgers New Jersey Med. Sch., Newark, NJ; [3]Rutgers Biomed. Hlth. Sci. - Newark, Newark, NJ

Abstract: Itch, or pruritus, is a significant side effect of neuraxial morphine therapy that often leads to cessation of opioid administration. Transient Receptor Potential Melastatin 3 (TRPM3) is a heat-activated ion channel expressed in various tissues, including peripheral sensory neurons of the dorsal root ganglia (DRG), spinal cord, and brain. Activation of opioid receptors and other Gi-coupled receptors, robustly inhibits TRPM3 through direct binding of G-protein βγ subunits to the channel protein. Even though Gβγ inhibition is robust and well-documented, its physiological relevance is not well understood. To better understand the in vivo relevance of this

inhibition, we generated a mouse model in which we deleted the exon encoding for the ten-amino-acid Gβγ binding site (TRPM3$^{\Delta Ex17}$). In DRG neurons of TRPM3$^{\Delta Ex17}$ mice, Ca^{2+} signals induced by the TRPM3 agonist pregnenolone sulfate (PregS) were not inhibited by the μ-opioid receptor agonist DAMGO, indicating that Gβγ inhibition is absent. Scratching behavior induced by intrathecal injection of morphine was significantly reduced in TRPM3$^{\Delta Ex17}$ mice compared to wild-type littermates. Intrathecal injection of the TRPM3 inhibitor primidone evoked itch, indicating that the channel inhibition is sufficient to induce itch by itself. Co-injecting PregS with morphine reduced itch, offering a potential therapy for opioid-induced itch. Itch induced by intradermal injection of DAMGO was also reduced in TRPM3$^{\Delta Ex17}$ mice. Intradermal primidone did not induce scratching behavior, indicating that TRPM3 inhibition alone is not sufficient to induce itch locally. Analgesia induced by systemic or intrathecal morphine on the other hand was largely maintained in TRPM3$^{\Delta Ex17}$ mice, indicating that Gβγ inhibition is dispensable for the analgesic effects of opioids.

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Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.02/B55

Topic: D.01. Somatosensation

Support: JSPS KAKENHI grant 22KJ2569

Title: The effect of heated propofol on the activation of human TRPA1

Authors: *C. SUDA[1], Y. TAKAYAMA[2], M. TOMINAGA[3], T. AKASE[1];
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Abstract: Propofol, an intravenous anesthetic, has a side effect of local pain at the injection site. Although various treatments for this pain have been investigated, this side effect has not been yet completely resolved. This pain is caused by propofol action on Transient Receptor Potential Ankyrin 1 (TRPA1), which is expressed in perivascular sensory nerve endings. While TRPA1 was initially reported to be activated by noxious cold stimulus, it has been recently understood that TRPA1 is a heat sensor. However, it is unclear whether propofol at different temperatures alters the pain intensity upon injection. Therefore, the aim of this study was to determine the effects of propofol at different temperatures on human TRPA1 activity. These findings may be useful for establishing a simple method of care to reduce vascular pain. Using HEK293T cells transfected with *hTRPA1*, membrane currents were measured with a whole-cell patch-clamp method. As propofol, 1% Diprivan® Injection (Sandoz K.K.) was diluted to 0.01 %. Intralipos® Injection 20 % (Otsuka Pharmaceutical Co., Ltd.) was used as the solvent and diluted to 0.1 %.

To evaluate the effect of temperature changes on hTRPA1, Diprivan was perfused after precooling or preheating the solution. First, the effect of Diprivan on hTRPA1 activity was examined in the range of approximately 10 - 45 °C. The results showed that the hTRPA1 currents activated by Diprivan were small at temperatures above 35 °C. Then, the effect of thermal stimulation on hTRPA1 activation by Diprivan was examined. The chamber solution was preheated to 35°C and then chilled to 25 °C before Diprivan application. The hTRPA1 currents were observed upon Diprivan application in this condition. Next, the chamber solution was preheated to 35 °C and then 35 °C or 25 °C Diprivan was applied. The hTRPA1 currents were smaller with 35 °C Diprivan than with 25 °C Diprivan. In the case of 35 °C Diprivan application, no AITC-induced responses were observed.
In this study, we found that hTRPA1 currents were very small when heated Diprivan (> 35 °C) was applied. The hTRPA1 can be actived by Diprivan when earlier heat-activated currents were inactivated by reduced solution temperature. This suggests that thermal stimulation may suppress pain induction by continued inhibition of hTRPA1 activation by propofol.

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Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

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Program #/Poster #: PSTR250.03/B56

Topic: D.01. Somatosensation

Support: NIH Grant 1R01NS115209

Title: Roles of TRP channels in spiking and calcium responses of cold nociceptors in Drosophila larva

Authors: *A. SAKURAI[1], N. V. MAKSYMCHUK[1], S. M. KOROGOD[2,1], Y. SHAMS[1], J. M. LETCHER[1], D. N. COX[1], G. S. CYMBALYUK[1];
[1]Georgia State Univ., Atlanta, GA; [2]Intl. Ctr. for Mol. Physiol., Kiev, Ukraine

Abstract: In *Drosophila* larvae, multidendritic primary sensory neurons tile the lumen of the body wall. In cold-nociceptive Class III (CIII) neurons, several TRP channels, including TRPA1 and PKD2, have been implicated in the cold-temperature sensitivity (Turner et al. 2016, Cox lab unpublished results). Here we conducted electrophysiological recording and Ca^{2+} imaging using CIII-specific expression of GCaMP6m and gene-specific RNAi knockdown of each TRP channel and further performed biophysical modeling to investigate the roles of TRP channels in encoding cold temperature.
CIII neurons exhibited a spiking response to rapid temperature decrease (2-6°C/sec) from 24°C to 10°C (Maksymchuk et al., 2022). Approximately half of the neurons showed bursts of spikes forming the spike rate peak. Following the peak, the spike rate settled at a lower steady-state frequency. In response to the temperature drop, we observed a rise of intracellular Ca^{2+},

beginning in the axon and then spreading to the cell body and dendrites. The axonal Ca^{2+} signal exhibited the highest rate of increase approximately 3 sec after the stimulus onset. In contrast, the cell body and dendrites showed slower Ca^{2+} responses, with the highest rate of increase occurring around 10 sec after the stimulus onset.
TRPA1-knockdown led to lower spike frequency than controls, accompanied by the reduced occurrence of bursts during the rapid temperature drop and markedly reduced the rate of rise in the soma Ca^{2+} signal. In contrast, PKD2-knockdown maintained initial bursting but showed significantly attenuated tonic spiking activity during the sustained low temperature; it did not affect the rate of rise in the soma Ca^{2+} signal but resulted in a significant increase in latency. Blocking action potentials with tetrodotoxin (TTX) diminished the axonal Ca^{2+} signal, but the soma and dendrites still exhibited Ca^{2+} signals of approximately half the original size. Both TRPA1- and PKD2-knockdown reduced the Ca^{2+} signals in TTX.
Based on the experimental results, we developed biophysical two-state models of the TRPA1 and PKD2 currents with their temperature-dependent activation as well as Ca^{2+}-dependent activation and inactivation processes. The model reproduced the CIII responses to the used temperature change protocols. The results highlight the critical role of TRPA1 in encoding the rate of temperature change with transient bursting activity, while PKD2 in sensing the temperature magnitude. The rise in intracellular Ca^{2+} concentration in the soma and dendrites appeared to originate mainly from axonal spiking and also via the TRPs-mediated Ca^{2+} influxes occurring independently of the spikes.

Disclosures: A. Sakurai: None. **N.V. Maksymchuk:** None. **S.M. Korogod:** None. **Y. Shams:** None. **J.M. Letcher:** None. **D.N. Cox:** None. **G.S. Cymbalyuk:** None.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.04/B57

Topic: D.01. Somatosensation

Support: Fisch College of pharmacy grant

Title: Antioxidant and cytoprotective effects of salvianolic acid derivatives on rat osteoblast cell

Authors: *A. KHAN[1,2], T. SARAVANAN[2], F. DEBA[2];
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Abstract: Osteoarthritis (OA) is a pervasive degenerative joint disorder which **is characterized by oxidative stress, synovial fluid inflammation, apoptosis in chondrocytes, cartilage degradation, bone sclerosis, and osteophyte formation.** Reactive oxygen species (ROS) production due to oxidative stress is the primary cause of many pathological disease processes. Approximately 32.5 million US adults are suffering from this disease. An understanding of molecular and cellular pathways and their association with joint tissues is necessary to develop

new therapeutic approaches for the prevention and treatment of OA. **Most of the** over-the-counter **non-steroidal anti-inflammatory drugs** are used to treat OA. Natural compounds with medicinal properties have been valuable and effective sources for the treatment of various diseases since ancient times. Salvianolic acid is one of the natural phenolic compounds of the plant Radix *Salvia miltiorrhiza* having antioxidant, anti-inflammatory, antimicrobial, anesthetic, and cytotoxic properties. There is a critical need for new drug planning to focus on the specific mechanisms of oxidative interaction in targeted TRPA1 ion channels and intracellular ion signaling, which will interact with other TRP channel subunits to regulate pathological diseases. In our experiment, we found that the rise of intracellular calcium ions in rat osteoblast cells due to excessive free radicals generated by H_2O_2 was suppressed by Salvianolic Acid-B. Therefore, this pilot project aims to identify Salvianolic acid analogs as lead compounds that target the TRP channel, which is one of the key pathway players in producing arthritis pain and other pathogenesis.

Disclosures: **A. Khan:** None. **T. Saravanan:** None. **F. Deba:** None.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.05/B58

Topic: D.01. Somatosensation

Support: Thompson Family Foundation Initiative in CIPN & Sensory Neuroscience
Howard Hughes Medical Institute

Title: Scn1b is required for proper mechanosensory signaling in mouse mechanoreceptors and nociceptors

Authors: *K. NGUYEN, Y. BABA, D. BAUTISTA, E. LUMPKIN;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Voltage-gated sodium channels (VGSC) are key regulators of neuronal excitability, and it is well-established that distinct subtypes of sensory neurons express different pore-forming alpha subunits. By contrast, we currently have little understanding of how modulatory beta subunits govern excitability in different sensory neuron subtypes. In a previous screen for genes that confer susceptibility to chemotherapy-induced peripheral neuropathy, a top hit was *Scn1b*, which encodes the β1 subunit of VGSC. SCN1B regulates the excitability of neurons and cardiomyocytes, and mutations in this gene underlie several rare human congenital diseases, including severe childhood epilepsies and cardiac dysfunction. Moreover, *Scn1b* global knockout mice die by P21 due to epilepsy. Recent studies show that *Scn1b* transcripts are highly expressed in touch receptors and proprioceptors of the dorsal root ganglia. To validate these findings, we used RNAscope to examine *Scn1b* expression in sensory neurons. *Scn1b* puncta were observed in all neurons but were enriched in the large-diameter myelinated subset as determined by co-

labeling with α-NEFH, a marker of myelinated neurons and an analysis of somatal diameters of *Scn1b*-positive and negative cells (median somatal diameter, *Scn1b*-pos.*:* 23 µm, n=185 neurons; *Scn1b*-neg.*:* 18 µm, n=132 neurons; P<0.0001, Mann-Whitney test). To determine the role of SCN1B in sensory neurons, we generated a somatosensory neuron-specific knockout of *Scn1b* by crossing $Scn1b^{fl/fl}$ mice with $Pirt^{Cre}$ mice. $Pirt^{Cre+};Scn1b^{fl/fl}$ conditional knockout (CKO) mice are viable, fertile and exhibit normal locomotor and exploratory behavior, as assessed with the open-field test (N=8 mice). Next, we assessed the effects of *Scn1b* deletion on A-fiber excitability using an *ex vivo* skin-saphenous nerve preparation. The mechanical threshold of A-fibers was significantly increased in CKO mice compared with littermate controls (CONT) (median von Frey threshold, CONT: 0.69 mN, N=4 mice, 66 fibers; CKO: 1.6 mN, N=8 mice, 57 fibers; P=0.002, Mann-Whitney). We also found that the instantaneous firing frequency was significantly lower in CKO mice compared with CONT (mean±SD, CONT: 215.6±186.7 Hz; CKO: 122.0±116.5 Hz; P=0.03; Student's t test, unpaired, two-tailed). By contrast, the mean conduction velocities of A-fibers did not differ between genotypes (P=0.56; Student's unpaired *t* test, two tailed). Together, these findings suggest that SCN1B is required to properly initiate mechanically evoked action potentials in mechanoreceptors and mechanonociceptors but has little effect on action potential propagation in these myelinated sensory afferents.

Disclosures: K. Nguyen: None. **Y. Baba:** None. **D. Bautista:** None. **E. Lumpkin:** None.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.06/B59

Topic: D.01. Somatosensation

Title: Molecular docking of capsaicin at epithelial membrane model TRPV1 receptor

Authors: *C. A. ZERÓN ALVARADO[1], A. CARRASCO CARBALLO[2], L. MARTÍNEZ MENDIETA[3], V. G. S. ALATRISTE BUENO[4];
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Abstract: The transient receptor potential vanilloid subtype 1 (TRPV1) is a transmembrane receptor with ion channel activity that allows the passage of cations, mainly calcium. The TRPV1 can be activated by capsaicin, the main component of chili peppers. The TRPV1 has been found on sensory fibers as well other cells. Different effects with respect to capsaicin concentration have been shown in different biological tissues. The TRPV1 activation by low concentrations of capsaicin promotes cell proliferation and differentiation, however high concentrations promote cell death. In the uterus, the expression of the TRPV1 has been demonstrated, but its function is poor understood. The uterus is an organ that is constantly undergoing regeneration, mainly luminal and glandular epithelial cells, so the TRPV1 may play

an important role in uterine cell development. In this work, an *in silico* molecular docking study was performed to identify the capsaicin binding site on the TRPV1 in an epithelial membrane model. The docking was performed on the Schrödinger platform. With the Protein Preparation Wizard tool, the crystallized structure of the tetrameric squirrel TRPV1 (PDB: 7LR0) was optimized to a physiological pH (pH=7.40). The capsaicin molecule (PubChem CID: 1548943) was loaded in Ligprep and macromodel tool. The probable binding areas such as the transmembrane and intracellular areas were selected in Glide tool by XP Molecular docking. Subsequently, the embedding of the TRPV1 in an epithelial membrane model was performed. The aims of embed the TRPV1 into an epithelial membrane was to assimilate *in vivo* molecular interactions in uterus. As a result, we found five capsaicin binding sites in the TRPV1 receptor. Four sites were found in the transmembrane zone with the following binding energies: Site 1: -8,092 Kcal/mol, Site 2: -8,097 Kcal/mol, Site 3: -7,078 Kcal/mol and Site 4: -7,598 Kcal/mol. One site was found in the cationic pore with a binding energy of -8,083 Kcal/mol. The dissociation constant (K_D) of each binding site was obtained with values of 2.0 μM, 2.0 μM, 10.4 μM, 4.5 μM and 2.0 μM respectively. According to our results, the sites with the best affinity are the transmembrane sites 1 and 2 and the cationic pore site. In our work we have found Different sites of activation for capsaicin in the TRPV1, we demonstrate the sensitivity for molecular interactions of the TRPV1 according to the concentration used. These results indicate possible reference capsaicin concentrations to test for TRPV1 stimulation in uterine cells.

Disclosures: C.A. Zerón Alvarado: None. **A. Carrasco Carballo:** None. **L. Martínez Mendieta:** None. **V.G.S. Alatriste Bueno:** None.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.07/B60

Topic: D.01. Somatosensation

Support: STEAM grant of NRF of Korea, RS-2023-00254795
NRF of Korea 2020R1A3A300192913
NRF of Korea 2020R1C1C101024513
NRF of Korea 2022M3E5E801739512

Title: Tentonin 3/TMEM150C comprises a pore-forming subunit with unique structure

Authors: *S. PAK, H. RYU, J. WOO, G.-S. HONG, K. HAN, T. KIM, U. OH;
Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

Abstract: Abstract : Tentonin 3(TTN3/TMEM150C) is a mechanosensitive (MS) channel with slowly-adapting (SA) kinetics. TTN3 mediates various physiological functions such as proprioception, baroreceptor reflex, and insulin secretion from pancreatic beta cells. Compared to other MS channels, TTN3 displays a unique biophysical property including the SA-type MS

currents as well as specific inhibition from a mutant conotoxin, NMB-1. Even with these distinctive characteristics, however, its role of as a *de novo* MS channel or molecular structure as an ion channel was not yet determined. When purified TTN3 proteins were incorporated to the lipid bilayer, spontaneous as well as stretch-induced single channel currents were evoked, suggesting that TTN3 forms a pore-forming, *de novo* MS channel. In addition, the Western blot analysis combined with crosslinking maneuver elicited a tetrameric complex of TTN3. A deep learning-based protein structure prediction algorithm, AlphaFold2, predicted a monomeric structure of TTN3. With this monomeric structure, molecular dynamics algorithms predicted several tetrameric configurations of TTN3. These putative configurations predicted key residues residing in the putative pore opening. We mutated these residues and selected one configuration whose mutation led to a complete blockade of mechanosensitivity. The selected tetrameric configuration showed a rectangular shape with a central pore. The transmembrane alpha helices, S1, S2, S5, and S6 of each subunit interact with the membrane lipids and surround the pore, whereas S3 and S4 constitute an ion conducting pathway. Mutations of residues lining the putative ion conducting pathway reduced MS channel currents. These results suggest that these residues are key components of an ion conducting pore and that the predicted structure may represent a native structure of TTN3.

Disclosures: S. Pak: None. **H. Ryu:** None. **J. Woo:** None. **G. Hong:** None. **K. Han:** None. **T. Kim:** None. **U. Oh:** None.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.08/B61

Topic: D.01. Somatosensation

Title: Comparative Transcriptome Profiling of Multiple Human Induced Pluripotent Stem Cell Derived Sensory Neuron Populations and Functional Validation of Pain Targets on Automated Patch Clamp Systems

Authors: *V. TRUONG[1], A. RANDOLPH[2], I. LU[2], R. CERONE[2], A. OBERGRUSSBERGER[3], R. HAEDO[2], T. STRASSMAIER[2], P. WALSH[1];
[1]Anatomic Inc., Minneapolis, MN; [2]Nanion Technologies, Livingston, NJ; [3]Nanion Technologies GmbH, Munich, Germany

Abstract: Nociceptors are a subset of sensory neurons that relay painful stimuli from the peripheral tissues. Multiple nociceptor subtypes exist and can respond to different thermal, mechanical, or chemical noxious stimuli. Recent findings with transcriptomics have identified gene expression patterns that classify these sub-types by different ion channels including Nav1.7, Nav1.8, Nav1.9, TRPV1, TRPA1, P2X3, HCN and a number of others that have been implicated in pain. In this study, we have identified a method to rapidly generate a novel TRPA1+ human induced pluripotent stem cell (hiPSC)-derived sensory neuron population and thoroughly

characterized it molecularly and functionally. Neurons were matured through four weeks and samples were processed on a weekly basis for bulk RNA sequencing and RNAscope. We found that this population was more similar to primary human DRG than other hiPSC-derived sensory neurons with RNA data sets publicly available, and specifically looked at differences in expression of ion channels, GPCRs, neuropeptides, and cell adhesion molecules. We also quantified this population via RNAscope and found 60% of the neurons express TRPA1+. Using high throughput automated patch clamp electrophysiology, we also explored properties of: voltage-gated sodium and potassium ion channels; TRP, GABA, and P2X ligand-gated ion channels; hyperpolarization-activated, cyclic nucleotide-gated channels; and mechanosensitive Piezo channels. Excitability properties in current clamp mode including resting membrane potential, spontaneous and evoked action potentials were also studied. These results were compared to a different hiPSC-derived sensory neuron population to determine the optimal sub-type and for target discovery and validation in high-throughput pain drug discovery screens.

Disclosures: **V. Truong:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **A. Randolph:** A. Employment/Salary (full or part-time):; Nanion Technologies. **I. Lu:** A. Employment/Salary (full or part-time):; Nanion Technologies. **R. Cerone:** A. Employment/Salary (full or part-time):; Nanion Technologies. **A. Obergrussberger:** A. Employment/Salary (full or part-time):; Nanion Technologies. **R. Haedo:** A. Employment/Salary (full or part-time):; Nanion Technologies. **T. Strassmaier:** A. Employment/Salary (full or part-time):; Nanion Technologies. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.09/B62

Topic: D.01. Somatosensation

Support: STEAM grant of the NRF of Korea RS-2023-00254795

Title: A specific blocker of Tentonin 3, NMB-1 and its blocking molecular mechanism

Authors: ***S. LIM**, U. OH;
Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Tentonin3 (TTN3/TMEM150C) is a mechanosensitive ion channel that exhibits unique biophysical, structural, and physiological functions distinct from Piezo channels. Notably, deep learning algorithms combined with molecular dynamics predict a putative TTN3 structure, which shows a tetramer with rectangular shape and a pore in the center. TTN3 elicits slowly-

adapting (SA) inactivation kinetics upon mechanical step stimuli. TTN3 mediates proprioception, baroreceptor reflex, and insulin release from pancreatic beta cells. Despite in depth studies on biophysical and functional aspects of TTN3, its specific inhibitor has not been identified. NMB-1, a conopeptide analogue, is known to selectively block the slowly adapting mechanically activated current in DRG neurons . As TTN3 confers SA-type mechanosensitive (MS) currents in DRG neurons , we hypothesized that NMB-1 may block TTN3. Indeed, NMB-1 blocked MS currents of TTN3. NMB-1, however, failed to block Piezo1 MS currents. Because NMB-1 is a conopeptide with 19 amino acids, we mutated functional residues such as bulky residues and positively charged residues to determine key residues for the blocking activity. Furthermore, we identified a structure of NMB-1 and predicted the location of its binding to TTN3. As TTN3 mediates numerous physiological functions, the identification of a specific blocker and its interaction mechanism would lead to the development of useful tools for clinical use.

Disclosures: **S. Lim:** None. **U. Oh:** None.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.10/B63

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant T32GM142605

Title: Lung-brain communication in the onset of respiratory viral infection

Authors: *S. MONROE[1], N. NANDURI[2], F. ULLOA SEVERINO[3], S. BILBO[2];
[1]Neurobiology, Cell. and Mol. Biol., [2]Duke Univ., Durham, NC; [3]Cell Biol. Dept., Duke Univ. Med. Ctr., Durham, NC

Abstract: Society faces increasing burden from respiratory immune challenge including respiratory viral infection. Respiratory viral infection, including with influenza A virus, can cause changes in brain function and understanding the link between lung and brain health is critical to anticipating the shifting health needs of our society. It is unknown how lung-brain communication impacts the progression of respiratory viral infection, or how different communication mechanisms are prioritized as inflammatory response progresses. Using a mouse model of infection with the influenza A strain PR8, this project explores immune signaling in either direction of the lung-brain axis. Preliminary data shows that during PR8 infection, changes in central nervous system (CNS) occur prior to inflammatory gene upregulation in lung tissue. The source and outcome of these acute phase CNS changes remains unknown. Pulmonary neuroendocrine cells are also the only cells in the lung epithelium directly innervated by the vagus nerve, making them a likely candidate to send rapid signals from the lung to the brain. PNECs can be manipulated by using cre-dependent tools in calca^{cre} mice to determine whether

these cells contribute to the CNS response to acute PR8 infection. Ablation of PNECs prior to infection reduces both proliferation of PR8 and inflammatory gene upregulation in lung tissue. This may also lead to a reduction in CNS response to infection. The ultimate role of CNS changes during acute PR8 infection remains unknown. Fos2A-iCreER (TRAP2) mice allow for the "capture" of neuronal ensembles using an inducible cre system to deliver a gene of choice. By delivering chemogenetic receptors to the neuronal population that responds to PR8, it is possible to later reactivate these neurons to determine whether they influence the immune outcome of infection. Preliminary data shows that the insular cortex has notable neuronal activity during the acute phase of PR8 infection, making it a promising region for implementation of this technique. Altogether, this research explores the connection between lung and brain health, focusing on these organs influence each other's immune states in the acute phase of respiratory infection.

Disclosures: S. Monroe: None. **N. Nanduri:** None. **F. Ulloa Severino:** None. **S. Bilbo:** None.

Poster

PSTR250. Ion Channels of the Peripheral Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR250.11/C1

Topic: D.02. Somatosensation – Pain

Support: NIH Grant R01DE026677
NIH Grant R35DE030045
NIH Grant R01DE031477
US Department of Defense Grant W81XWH-22-1-0076

Title: Unraveling itch and pain sensations by in vivo voltage imaging

Authors: *Y. ZHANG[1], H. SON[1], J. SHANNONHOUSE[1], R. GOMEZ[1], M.-K. CHUNG[2], J. PLATISA[3], V. A. PIERIBONE[4], Y. KIM[1];
[1]The Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [2]Univ. of Maryland Dent. Sch., Univ. of Maryland Dent. Sch., Baltimore, MD; [3]The John B Pierce Lab., New Haven, CT; [4]Yale Univ., Yale Univ., New Haven, CT

Abstract: Both itch and pain are unpleasant sensations caused by exposure to certain chemical irritants, injuries, or inflammation. Despite itch and pain sensations being distinguishable in behavioral readouts, itch and pain signals are difficult to discern in functional studies with traditional electrophysiology and calcium imaging due to similar discharge patterns, represented as action potentials and intracellular calcium transients, respectively. Thus, little is known of how somatosensory neurons transmit and process itch and pain information *in vivo*. Here, we generated and characterized a knock-in mouse line with Pirt-driven expression of Marina, a positively tuned genetically-encoded voltage indicator, in primary sensory neurons. Pirt-Marina mice enable optical reporting of touch, itch, and nociceptive sensations *in vivo* and subtype-

specific action potential patterns in the trigeminal and dorsal root ganglia neurons. Our results suggest that neuronal firing encoded by noxious or pruritic stimuli are processed differently when they pass through soma of primary sensory neurons within ganglia. The pain signals are encoded by neuronal action potential firing activity, but itch sensations are by variable subthreshold voltage dynamic changes and their summation. This novel Pirt-Marina mouse line provides optical access to dynamic neuronal activity and plasticity in the peripheral nervous system with high temporal accuracy, fidelity, and reliability, greatly expanding our knowledge of how somatosensory neurons differentiate and encode itch, pain, and other sensations in live animals.

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Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.01/C2

Topic: B.03. Ion Channels

Support: Israel Science Foundation (grant No. 1384/19)

Title: Resurrected from obscurity: the forgotten Goldman-Hodgkin-Katz (GHK) current equation: stable spike firing in ultrathin axons.

Authors: *O. KOTLER[1], M. GUTNICK[2], I. FLEIDERVISH[1];
[1]Physiol. and Cell Biol., Ben Gurion Univ. of the Negev, Beer Sheva, Israel; [2]Koret Sch. of Vet. Med., Hebrew Univ. of Jerusalem, Rehovot, Israel

Abstract: In the 1940s, two equations emerged that describe the relationships between current and voltage across a membrane. The more famous equation, the GHK *voltage* equation, reconciled the Nernst potentials of the various ion species with their partial permeabilities. The less famous GHK *current* equation described the non-linear relationship between current and voltage for different concentration gradients. Hodgkin and Huxley, who did not benefit from modern computers, knew the GHK current equation and its ramifications. However, they preferred to use a simplified linear model for their equations, and this estimation fit their data well. Recently, several studies have used the Hodgkin-Huxley style linear conductance models to study the excitable properties of very thin axons. They found that high-frequency repetitive firing in these fibers could cause the Na^+ concentration gradient to dissipate, drastically compromising spike generation and propagation. However, we now show that when the current-voltage relationship is described using the GHK current equation, the Na^+ current in the voltage range relevant to the action potential (AP) generation is barely affected by dramatic changes in $[Na^+]_i$. Thus, whereas the linear model predicts that a 10-fold increase in $[Na^+]_i$ leads to an 80% decrease in inward current at 0 mV and an equivalent slowing of the rate-of-rise of an AP, the

non-linear GHK current equation predicts only ~ 20% change. This dramatic difference is significant because so much of the recurrent activity in many brain areas is via axons with diameters less than 0.5 microns. Since experimental access to these compartments is very limited, we must rely on computational models for insight. In summary, by placing the voltage range of the AP in a region that is relatively resistant to changes in Na^+ concentration gradient, evolution has ensured stable interaction of neurons in highly active complex local networks.

Disclosures: O. Kotler: None. **M. Gutnick:** None. **I. Fleidervish:** None.

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.02/C3

Topic: B.03. Ion Channels

Support: NIH R44 MH119842-02

Title: Using Real-Time Dynamic Clamp to Determine the Effects of State-Dependent Toxin Action on Action Potential Behavior in Living Neurons

Authors: B. K. PANAMA[1], ***M. W. NOWAK**[2], S. ACHARYA[2], C. BASS[2], L. KORBEL[2], R. L. RASMUSSON[2,1], G. C. L. BETT[2,1];
[1]Jacobs Sch. of Med., SUNY at Buffalo, Buffalo, NY; [2]Cytocybernetics, Pendleton, NY

Abstract: Ion channel dysfunction leading to aberrant neuronal function underlies many neurological diseases (e.g., epilepsy, neuropathic pain) and Pharma has devoted considerable effort in developing drugs targeting ion channels. A critical aspect is understanding which ion channel state (closed, open, inactive) must be blocked in order to normalize neuronal function. The aim of these studies is to utilize real-time dynamic clamp to express virtual sodium channel models of state-dependent drug block into living neurons and assess the effects on action potential (AP) behavior. We compared the effects of the late Na channel current potentiator ATX-II with virtual expression of a neuronal Na channel with a persistent late current model (I_NaP, Herzog et al., 2021) on AP behavior in human pluripotent stem cell-derived GABAergic neurons (hiPSC-GNs) (iCell-GABA Neurons, Fujifilm Cellular Dynamics Inc, Madison, WI). Electrophysiological recordings were performed using the whole-cell ruptured patch clamp configuration and real-time dynamic clamp was implemented using the Cybercyte system (Cytocybernetics, Inc., Buffalo, NY). As with previous studies, due to the lack of expression of background K^+ currents, the stable recording of APs in hiPSC-GNs required the electronic expression of a Goldman-Hodgkin-Katz outwardly rectifying K^+ current to adjust the depolarized resting membrane potential (RMP) (29.4±1.2 mV, n=21) to a more physiological value (60.5±0.5 mV, n=21). This allowed for the recording of stable evoked APs (stimulus: 0.3-1.0 nA for 0.3-1.5 ms). APs measured in the presence of 100 nM ATXII altered the AP morphology with a significant prolongation of the AP duration at 90% repolarization (APD90)

(Control: 6.3±1.0 ms, ATXII: 12.4±2.6 ms, n =4, paired t-Test, $p<0.05$). To model the effect of ATXII, we blocked the endogenous Na current with 100 nM TTX and virtually expressed I_NaP. Similar to ATX-II, INaP virtual expression also altered AP morphology and prolonged the APD90 (Control: 12.3±3.3 ms, INaP: 43.5±8.1 ms, n =6, paired t-Test, $p<0.05$). Our data demonstrate that dynamic clamp can be utilized to determine the effects of state-dependent toxin action on neuronal AP behavior. Further studies will examine the effects of virtual expression of Markov I_Na models with state-dependent actions on neuronal AP behavior. This approach can be utilized in developing drugs that target ion channels in which efficacy and normalization of aberrant neuronal function are dependent on block of a specific ion channel state.

Disclosures: B.K. Panama: None. **M.W. Nowak:** A. Employment/Salary (full or part-time):; Cytocybernetics. **S. Acharya:** A. Employment/Salary (full or part-time):; Cytocybernetics. **C. Bass:** A. Employment/Salary (full or part-time):; Cytocybernetics. **L. Korbel:** A. Employment/Salary (full or part-time):; Cytocybernetics. **R.L. Rasmusson:** A. Employment/Salary (full or part-time):; Cytocybernetics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cytocybernetics. **G.C.L. Bett:** A. Employment/Salary (full or part-time):; Cytocybernetics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cytocybernetics.

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.03/C4

Topic: B.03. Ion Channels

Support: R01DC016324

Title: Presynaptic leak channel NALCN regulates vesicular glutamate transport and vesicle release

Authors: *T. WU, D. LI, Y. DARWISH, T. XIAO, H. HUANG;
Tulane Univ., New Orleans, LA

Abstract: At chemical synapses, Ca^{2+} triggers and modulates neurotransmitter release. The action potential-triggered high-concentration Ca^{2+} transients are required for rapid exocytosis, while a low concentration of basal Ca^{2+} can modulate subsequent release via vesicle recruitment, priming and sensitization, thus controlling the strength of synaptic transmission. The Ca^{2+} channels activated by action potentials that trigger neurotransmitter release have been extensively studied. However, little is understood about the ion channel that sets resting Ca^{2+} level and modulates neurotransmitter release, especially at glutamatergic synapse. Here we report that the Na^{+} leak channel, non-selective (NALCN) is expressed in the calyx of Held terminals and controls the presynaptic resting membrane properties. NALCN is Na^{+}-permeable

that controls the presynaptic resting Na^+ level and, by activating vesicular Na^+/H^+ exchanger, regulates vesicular glutamate transport. NALCN is also Ca^{2+}-permeable and regulates resting Ca^{2+} level and glutamate release. NALCN is tightly coupled with release machinery and regulates both the amplitude and frequency of miniature excitatory postsynaptic current (mEPSC). Moreover, blocking NALCN decreases synaptic strength and disrupts reliable neurotransmission during prolonged high-frequency signaling. Therefore, this work demonstrates that the activity of presynaptic NALCN regulates both vesicular glutamate transport and neurotransmitter release in the mammalian central nervous system.

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Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.04/C5

Topic: B.03. Ion Channels

Support: TUBITAK
DAAD

Title: Exploring Time-Dependent Modulation of Active Zone Protein Accumulation by the NALCN Channel Pore Unit

Authors: *R. KARATEPE;
Univ. of Hlth. Sci., Istanbul, Turkey

Abstract: Synaptic dysfunction has been implicated in a range of neurological disorders, including epilepsy, movement disorders, and intellectual disability. At our institute, we have identified several patients harboring mutations in genes that have the potential to be important players in synapse function, NALCN channel being one of them.NALCN channel is a sodium leak channel composed of the NALCN protein, which forms the pore region, and two accessory subunits, UNC80 and UNC79. Previous research has demonstrated that NALCN leak channel localizes to synapses in Drosophila, and disruption of its components leads to altered locomotor activity and disturbances in circadian rhythm.The objective of this study was to investigate the impact of silencing the pore region of the sodium leak channel NALCN on synaptic protein abundance. To achieve this, we employed immunohistochemistry and imaging techniques using Drosophila larvae as a model organism. By silencing the expression of the NALCN channel pore region, specifically the NALCN ortholog na, in motoneurons, we aimed to identify changes in synaptic protein intensity and synapse (active zone) number.While the number of active zones remained constant in both the motoneuronally silenced na larvae and the wild-type larvae, we observed time-dependent oscillation of synaptic marker bruchpilot (brp) and glutamate receptors, at the neuromuscular junction. Surprisingly, this oscillatory pattern was reversed when silencing the NALCN ortholog na in motor neurons.Our findings indicate that the NALCN channel

component na plays a crucial role in regulating time-dependent levels of brp and glutamate receptors in Drosophila. Understanding the mechanisms underlying these changes could provide valuable insights into the pathogenesis of some synaptic disorders.

Disclosures: R. Karatepe: A. Employment/Salary (full or part-time):; FMP and University of Health Sciences. 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.; TUBITAK. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); DAAD.

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR251.05/C6

Topic: B.03. Ion Channels

Support: National Institutes of Health Grants R35 NS122073
Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Simplified AAV production protocols for neuroscience research

Authors: *Y. OGAWA[1], M. N. RASBAND[2];
[1]Baylor Col. of Med., Houston, TX; [2]Neurosci., Baylor Col. of Med. Dept. of Neurosci., Houston, TX

Abstract: The axon initial segment (AIS) is important for the generation and propagation of action potentials, and regulation of neuronal polarity. Although it is well established that AnkyrinG (AnkG) and β4-Spectrin play key roles in the formation and maintenance of the nodes of Ranvier and AIS, the molecular composition of these domains remains incompletely understood. We recently used proximity biotinylation and proteomics approaches to identify candidate AIS and nodal proteins. To validate and investigate these candidates, we developed an AAV-mediated CRISPR-based genome editing method which allows for high-throughput analysis in both cultured neurons and brain. Using this high-throughput knock-in screening strategy, we found several new AIS proteins. For subsequent functional analysis of these new AIS proteins, we also developed a simplified AAV production method which allows high-throughput and efficient knockout or overexpression in cultured neurons. Together, these methodologies are flexible and efficient for the analysis of proteins associated with a variety of subcellular structures and can be used to address a broad spectrum of neurobiological questions.

Disclosures: Y. Ogawa: None. **M.N. Rasband:** None.

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.06/C7

Topic: B.03. Ion Channels

Title: Biophysical properties of sodium channels in dopaminergic midbrain neurons defined by axonal projections.

Authors: *M. JAHNKE[1], J. MANKEL[2], J. ROEPER[2];
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Abstract: The midbrain dopamine (DA) system is critical for various essential brain functions such as working memory, movement control, motivation, and reward-based learning. Dysfunction of distinct DA subpopulations respectively contributes to major disorders such as Parkinson disease, schizophrenia, or drug addiction. Midbrain DA neurons release DA within their specific axonal target areas, which include the nucleus accumbens (NAc) subregions and the dorsal striatum. DA levels in these areas depend on both the action potential discharge patters in the projecting DA neurons and local control mechanisms at the distal axon. To further define the biophysical properties of projection-specific DA subpopulations we studied their respective voltage-gated sodium (Na^+) channels.Using nucleated outside-out patches previous studies investigated the differences between the functional characteristics of voltage-gated Na^+ currents in midbrain GABAergic and DA neurons (Seutin and Engel., 2010; Ding et al., 2011) and DA neurons of the ventral tegmental area (VTA) and substantia nigra (SN) (Yang et al., 2019). However, sodium current properties of projection-defined DA subpopulations have yet to be described. For that purpose, we combined axonal retrograde tracing with nucleated outside-out patch clamp recordings of labelled DA neurons in adult male C57Bl6N mice.As a first step, we recorded voltage-gated Na^+ currents of NAc-core and NAc-medial shell-projecting DA subpopulations. These two subpopulations in the VTA both belong to a extended-firing range DA phenotype (Lammel et al., 2008, Knowlton, Ziouziou et al. 2021). As expected we observed no significant differences in the functional properties of their Na^+ currents (activation 10-90% rise time (at - 20 mV): NAc-core: 263.2 ± 43.5 µs, n = 11, N = 4; NAc-medial shell: 251.1 ± 36.6 µs, n = 22, N = 5; p = 0.84; inactivation 10-90% rise time (at - 20 mV): NAc-core: 2.12 ± 0.71 ms, n = 11, N = 4; NAc-medial shell: 4.16 ± 0.8 ms, n = 21, N = 5; p = 0.1; Na^+ current density (at - 20 mV): NAc-core: 22.6 ± 8.1 pA/pF, n = 10, N = 4; NAc-medial shell: 27.5 ± 4.4 pA/pF, n = 21, N = 5; p = 0.57). Next, we will explore Na^+ current properties in nucleated outside-out patches of NAc-lateral shell-projecting DA neurons, which are a distinct VTA/SN DA subpopulation characterized by a compressed firing-range phenotype.

Disclosures: M. Jahnke: None. **J. Mankel:** None. **J. Roeper:** None.

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.07/C8

Topic: B.03. Ion Channels

Support: NIH Grant No. T32AG0679 (T.J.B.)
NIH grants R01MH124351; R01ES031823; R01ES031823-03S1, (F.L.)
Houston Area Molecular Biophysics Program Grant No. T32 GM008280 (N.M.D).

Title: Pharmacologically Targeting the Nav1.6:GSK3β Protein Complex to Mitigate Hyperexcitability in Early-Stage Alzheimer's Disease

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Abstract: Despite global initiatives to elucidate the pathophysiology of Alzheimer's disease (AD), there is an unmet need for disease-modifying AD therapeutics. Numerous studies show a causal relationship between hippocampal hyperactivity and the onset of cognitive impairments during early-stage AD. Voltage-gated Na+ channels (Nav channels) are transmembrane proteins with critical regulatory roles in synaptic function and neuronal firing. Importantly, Nav1.6 plays a critical role in action potential initiation due to its localization at the axon initial segment, and therefore serves as an attractive target for modulation of neuronal excitability. The Nav1.6 channel is regulated through its interactions with various auxiliary proteins and signaling molecules. Studies from our lab revealed that glycogen synthase kinase 3β (GSK3β) directly binds and phosphorylates the Nav1.6 C-terminal domain (CTD), indicating that GSK3β regulates the Nav1.6 channel via a dual-function mechanism including phosphorylation and complex formation. Functionally, genetic silencing of GSK3β suppresses Nav1.6-encoded currents, while GSK3β overexpression stimulates Nav1.6 activity and promotes maladaptive firing of neurons. Critically, overexpression and dysregulation of GSK3β is observed in the hippocampus of AD brains. This evidence suggests that dysregulated GSK3β-mediated modulation of Nav1.6 facilitates neuropathological phenotypes associated with the early-stage AD. Using the split-luciferase complementation assay, we have identified a small molecule ligand, 1063, that significantly inhibits Nav1.6:GSK3β complex assembly compared to vehicle control. Furthermore, 1063 reduces Nav1.6-mediated sodium currents in a manner reminiscent of GSK3β knockdown. Using *ex vivo* patch clamp electrophysiology in 2-4 month old 3x-Tg-AD mice, we show that hyperexcitability in the CA1 region of the hippocampus is mitigated with knockdown of GSK3β, and that the effects of 1063 in this region are dependent on the presence of GSK3β. Mutagenesis screening indicated that the Nav1.6:GSK3β complex is mediated by residues of the GSK3β axin-binding domain. Functional studies revealed that expression of the GSK3β axin-binding domain is sufficient to inhibit GSK3β-induced upregulation of Nav1.6-mediated currents in heterologous cells, suggesting that residues within this region are required for GSK3β's functional effects on the channel. Cooperatively, these results illustrate a novel, druggable interface between Nav1.6 and GSK3β that holds potential as a disease-modifying target for early-stage AD.

Disclosures: **T.J. Baumgartner:** None. **N.M. Dvorak:** None. **N.A. Goode:** None. **A.K. Singh:** None. **Z. Haghighijoo:** None. **Z. Haghighijoo:** None. **P.A. Wadsworth:** None. **F. Laezza:** Other; Founder and President of IonTx Inc..

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.08/C9

Topic: B.03. Ion Channels

Support: NIH Grant NS027881

Title: Possible roles for the sodium leak channel (Nalcn) in serotonergic (5-HT) dorsal raphe (DR) neurons: Implications for hypocretin/orexin (OxR) and alpha1 (Adra1) receptor signaling

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Abstract: Serotonergic DR neurons provide extensive ascending innervation of brain regions that influence many functions including those that regulate mood, reward, feeding and metabolism, sleep and arousal, and sensory and motor systems. Moreover, regulation of extracellular 5-HT levels is critically implicated in the etiology and treatment of major psychiatric illness, including depression. Thus, factors that influence the firing of these neurons will widely impact CNS function. The orexin/hypocretin and noradrenergic systems can potently depolarize and induce firing in these 5-HT neurons by GPCR-activation of noisy cation-permeable ion channels that are effectors for the convergent signaling of OxRs and Adra1 on these neurons, although the identity of these channels is not known. By leveraging published gene expression profiles of 5-HT neurons, we identified several candidate cation channels including the sodium leak channel (Nalcn), which regulates resting membrane potential and can couple to GPCRs to alter neuronal excitability in some neurons. Initial immunocytochemistry experiments suggested that Nalcn protein is present in serotonergic DR neurons. However, subsequent knockout experiments utilizing AAV delivery of Cre-recombinase to $Nalcn^{fl/fl}$ mice revealed an incomplete absence of Nalcn immunostaining in Cre-expressing neurons, suggesting a lack of antibody specificity. To test for the presence of functional Nalcn channels, we are using whole-cell patch clamp recordings from DR neurons in brain slices obtained from $Nalcn^{fl/fl}$ mice. Our preliminary data indicate the presence of a small TTX-insensitive, Na^+-dependent current (12.3 ± 2.2 pA, N = 5) at -70 mV in putative 5-HT DR neurons, which was revealed by lowering extracellular Na^+ from 151.2 mM to 27.2 mM with NMDG substitution in the ACSF. This Na^+-dependent current was increased to 39.8 ± 6.1 pA at -70 mV (N = 5) following application of the Adra1 agonist phenylephrine (3 uM). To determine if these currents are mediated by Nalcn, we are now examining these currents in mice selectively lacking Nalcn in 5-HT neurons. We anticipate these findings will delineate the potential roles of Nalcn in regulating membrane

potential and excitability of 5-HT DR neurons. Understanding these molecular mechanisms could therefore provide valuable therapeutic targets for modulating the many functions engaged by 5-HT DR neurons.

Disclosures: **S. Javed:** None. **E. Berry:** None. **M. Ishibashi:** None. **C.S. Leonard:** None.

Poster

PSTR251. Sodium Channels

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Program #/Poster #: PSTR251.09/C10

Topic: B.03. Ion Channels

Support: NIH Grant R01MH095995

Title: Modulation of voltage-gated sodium (Na_v) channel inactivation, medium spiny neuron excitability, and motivation-related behavior through pharmacologically targeting the $Na_v1.6$/fibroblast growth factor 14 complex

Authors: *N. M. DVORAK[1], P. A. WADSWORTH[1], D. S. ENGELKE[2], A. SINGH[1], N. NGUYEN[3], P. WANG[1], H. CHEN[1], R. T. POWELL[3], C. STEPHAN[3], F. DO MONTE[2], J. ZHOU[1], F. LAEZZA[1];
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Abstract: Voltage-gated Na^+ (Na_v) channels enable the initiation and propagation of action potentials. While the α subunit is sufficient for ion conduction, the full physiological function of Na_v channels is dependent upon protein:protein interactions (PPI) with auxiliary proteins. In the brain, $Na_v1.1$, $Na_v1.2$, and $Na_v1.6$ are the primary isoforms expressed, and they differ with respect to their cellular and subcellular distributions. In medium spiny neurons (MSN) of the nucleus accumbens, which is a central hub of reward circuitry, the $Na_v1.6$ channel is the primary isoform expressed and its activity is regulated by the auxiliary protein fibroblast growth factor 14 (FGF14). Here, we explore the druggability of the FGF14/$Na_v1.6$ complex in an effort to fine-tune reward circuitry that is corrupted in an array of psychiatric disorders. To that end, we screened ~45,000 small molecules for effects on FGF14/$Na_v1.6$ complex assembly. In cell screening, in tandem with protein:ligand binding studies, functional validation modules, and molecular modeling, identified a class of four compounds targeting the intermolecular interaction between $FGF14^{R117}$ and the $Na_v1.6^{D1846:R1866}$ salt bridge. From this class, 1028 was selected as the representative ligand on account of its superior potency. Mutation studies revealed that 1028 modulated FGF14/$Na_v1.6$ complex assembly through a mechanism dependent upon an intact interaction between $FGF14^{R117}$ and the $Na_v1.6^{D1846:R1866}$ salt bridge. Functionally, 1028 was shown to cause a depolarizing shift in the voltage-dependence of inactivation of $Na_v1.6$-mediated sodium current through a mechanism dependent upon an intact interaction between the III-IV

linker and C-terminal domain. 1028's effects on $Na_v1.6$ channel inactivation correspondingly resulted in increased activity of MSNs *ex vivo* and *in vivo*. Behaviorally, electrophysiological changes conferred by 1028 were shown to correlate with alterations in behaviors associated with motivation. Collectively, these results demonstrate that the FGF14/$Na_v1.6$ complex is amenable to small molecule modulation and that it could serve as a therapeutic target for psychiatric disorders.

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Poster

PSTR251. Sodium Channels

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Program #/Poster #: PSTR251.10/C11

Topic: B.03. Ion Channels

Support: R01MH124351
R01MH132226
U18DA052504

Title: Fgf14 derived ligand differentially regulates $na_v1.2$ and $na_v1.6$ function

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Abstract: Voltage-gated Na^+ channels (Na_v) are the molecular determinants of action potential initiation and propagation because of their role in mediating ionic flow (Na^+). Among the nine voltage-gated Na^+ channels, $Na_v1.2$ and $Na_v1.6$ are of particular interest in the central nervous system because of their role in modulating forward ($Na_v1.6$) and backward ($Na_v1.2$) action potential propagation. In pyramidal neurons, the interplay between $Na_v1.2$ and $Na_v1.6$ is complex with reduction or complete loss of $Na_v1.2$ producing a paradoxical increase in excitability, contrary to the reduction of excitability observed when $Na_v1.6$ is absent. Although the α-subunit can sufficiently confer transient Na^+ currents (I_{Na}), in vivo these channels are modulated by auxiliary proteins like intracellular fibroblast growth factor 14 (FGF14) through protein:protein interactions (PPIs). Previous studies have identified ZL0177, an FGF14 ligand derived from a short amino acid sequence mapped to the FGF14/$Na_v1.6$ PPI, as a functional modulator of $Na_v1.6$. In this report, ZL0177 was chosen for selectivity evaluation against $Na_v1.2$ and $Na_v1.6$. We observed statistically significant changes in peak I_{Na} density as well as shifts in both $V_{1/2}$ of activation and steady-state inactivation that were isoform specific. To that end, ZL0177

effectively decreased $Na_v1.6$ and $Na_v1.2$ mediated peak I_{Na} density, while causing statistically significant shifts in $V_{1/2}$ of activation that were isoform specific when compared to their corresponding controls. In addition, ZL0177 caused a selective shift in $V_{1/2}$ of steady-state inactivation for $Na_v1.2$, with no effect in $Na_v1.6$. Computational investigations using AlphaFold (AF) models of $Na_v1.2$ and $Na_v1.6$ revealed isoform specific interactions of ZL0177 with the inactivation gate and C-terminal domain (proximal:$Na_v1.2$ vs. distal: $Na_v1.6$). Complementary computational neuronal models of pyramidal neurons predict that ZL0177 results in distinct phenotypic variations in intrinsic excitability by selectively modulating $Na_v1.2$ and $Na_v1.6$ in an isoform specific manner. These findings support the distinct roles of $Na_v1.2$ and $Na_v1.6$ channels, raising the need for the development of isoform-specific probes to interrogate Nav channel function *in vivo*.

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Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.11/C12

Topic: B.03. Ion Channels

Support: NRF-2016R1A2B4011333
NRF-2018R1A6A1A03025108

Title: Mechanism of inhibition by polysorbate 80 on the sensory and cardiac sodium channels

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Abstract: Polysorbate 80 (PS80) is a non-ionic detergent derived from polyethoxylated sorbitan and oleic acid. It is widely used in pharmaceuticals, foods, and cosmetics as an emulsifier. $Na_v1.7$ is a peripheral sodium channel that is highly expressed in sympathetic and sensory neurons, and it plays a critical role in determining the threshold of action potentials (APs). We found that PS80 either abolished APs or increased the threshold of the APs of dorsal root ganglions. We thus investigated whether PS80 inhibits $Na_v1.7$ sodium current using a whole-cell patch-clamp recording technique. Also, we wondered whether PS80 has similar effects on $Na_v1.5$ sodium current important for generating action potentials in cardiomyocytes. PS80 decreased the peak currents in a concentration-dependent manner on both channels, and the

inhibition by PS80 was more potent when the holding potentials were more depolarized. The blocking of $Na_v1.7$ and $Na_v1.5$ currents by PS80 was not reversible at a holding potential of −90 mV but completely reversible at −120 mV, where the channels were mostly closed. The activation rate and the voltage dependency of activation curves for $Na_v1.7$ and $Na_v1.5$ were not changed by PS80. However, PS80 hyperpolarized the voltage dependency of the steady-state inactivation curves, slowed the recovery from inactivation, and produced robust use-dependent inhibition, suggesting it preferentially binds to the inactivated state. Our results indicate that PS80 has concentration-, state-, and use-dependent inhibitory effects on $Na_v1.7$ and $Na_v1.5$ channels, which may have potential implications for the peripheral nervous system and cardiac function even below commercial concentrations.

Disclosures: R. Kim: None. **J. Choi:** None.

Poster

PSTR251. Sodium Channels

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Topic: B.03. Ion Channels

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NIH U18DA052504 (FL)
HAMBP training grant no. T32GM008280 (NMD)

Title: Peptide-based probe reveals a scaffolding function of GSK3β in the Nav1.6 macromolecular complex

Authors: *A. K. SINGH, N. M. DVORAK, Z. HAGHIAHIJOO, M. BERNABUCCI, J. SINGH, Z. LIU, Y. XUE, J. ZHOU, F. LAEZZA;
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Abstract: Kinase signaling pathways regulating ion channel macromolecular complexes play a crucial role in fine-tuning neuronal activity and remodeling synapses. Yet, the molecular underpinnings of activity-dependent signaling mechanisms regulating these molecular complexes are still poorly understood. In recent studies conducted in the nucleus accumbens (NAc), we have shown that vulnerability to depression-like and stress-induced disorders induces a form of maladaptive plasticity consisting of hyperexcitability of medium spiny neurons (MSNs). Vulnerability in these cells is mediated by the increased interaction between glycogen synthase kinase 3β (GSK3β) and the C-terminal domain (CTD) of the voltage-gated Na+ channel Nav1.6. A decoy peptide mimicking the Nav1.6 segment interacting with the kinase or in vivo genetic silencing of GSK3β were found to be sufficient to prevent MSN maladaptive plasticity. Building

on these results, we hypothesized that inhibition of the GSK3β/Nav1.6 protein-protein interaction complex could counteract GSK3β-dependent maladaptive plasticity of MSNs. To that end, we developed a series of peptide-based probes capable of modulating the scaffolding function of GSK3β in the Nav1.6 channel complex. Molecular docking, split-luciferase complementation (LCA), intrinsic fluorescence, surface plasmon resonance (SPR), whole-cell patch-clamp electrophysiology in heterologous cells, and in the ex-vivo acute slice preparation as well as viral vector-based in vivo gene silencing were implemented for discovery and validation studies. Probe ZL141 was found to significantly inhibit GSK3β/Nav1.6 complex formation using the LCA and to bind to GSK3β using SPR. In addition, whole-cell patch-clamp recordings in HEK293 cells stably expressing Nav1.6 showed that ZL141 regulates peak current density, voltage-dependent activation, and steady-state inactivation curves as well as long-term inactivation of Nav1.6 in a GSK3β-dependent manner. Preliminary studies employing GSK3β in vivo genetic silencing and ex vivo slice recordings of MSN in the NAc support the mechanism of action of ZL141 observed in heterologous cells. These studies lay the groundwork for the development of novel neurotherapeutics based on modulation of non-enzymatic activity of GSK3β in the brain.

Disclosures: **A.K. Singh:** A. Employment/Salary (full or part-time):; Pharmacology & Toxicology, Mental Health Research Group. **N.M. Dvorak:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); HAMBP training grant no. T32GM008280 (NMD). **Z. Haghiahijoo:** None. **M. Bernabucci:** None. **J. Singh:** None. **Z. Liu:** None. **Y. Xue:** None. **J. Zhou:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); R01 MH111107 (F.L., J.Z.), R01 DA038446 (JZ). **F. Laezza:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIH Grant NIH R01MH124351 (FL), R01MH132226 (F.L.), R01 MH111107 (F.L., J.Z.), U18DA052504 (FL).

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.13/C14

Topic: B.03. Ion Channels

Support: R35HL155671

Title: Inhibition of Sympathetic Nerve Mediated Contraction of Human and Guinea Pig Blood Vessels by Selective $Na_V1.7$ Blockers

Authors: *J. S. KIM[1], S. MEEKER[1], T. S. ZABKA[2], D. H. HACKOS[2], B. J. UNDEM[1]; [1]Med., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Genentech Inc, South San Francisco, CA

Abstract: We quantified the effect of blocking $Na_V1.7$ with two highly selective $Na_V1.7$ blockers on sympathetic nerve-evoked adrenergic contractions of blood vessels isolated from guinea pigs and humans. We isolated pulmonary arteries from human lungs (obtained via NIAA) and the abdominal aorta from guinea pigs. The smooth muscle tension was quantified using standard tissue bath technology. The intrinsic nerves were stimulated with electrical field stimulation (EFS, 12V, 1msec, 10Hz) for 30 sec. This causes rapid contraction in all tissues, which was entirely prevented with alpha adrenoceptor antagonists (1 μM prazosin). The contractions were quantified as the % of a maximal obtainable adrenergic contraction evoked by 100 μM phenylephrine added at the end of the experiment. Genentech Pharmaceuticals provided a highly selective $Na_V1.7$ blocker (GNE8493; 500-5000 fold selective for $Na_V1.7$ over other Na_Vs), while SiteOne Pharmaceuticals provided another mechanistically distinct, highly selective $Na_V1.7$ blocker (ST2262; 1000-fold selective for $Na_V1.7$ over other Na_Vs) (Sci Rep. 10:14791, 2020). We previously published that the parasympathetic neurons in human and guinea pig airways express only $Na_V1.7$, making the parasympathetic cholinergic contractions of the airways a useful tissue level "bioassay" for $Na_V1.7$ activity (see JPET,361: 172-180, 2017). The potencies (-log M IC_{50}) of GNE8493 and ST2262 at blocking $Na_V1.7$- dependent parasympathetic contractions of human bronchi averaged 6.7 ± 0.4 (n=8) and 6.2 ± 0.1 (n=13), respectively. The EFS-induced activation of sympathetic nerves caused contractions of human pulmonary arteries averaging 12 ± 3% and 0.7 ± 0.3% in the absence and presence of GNE 8493, respectively ($P<0.01$); and 8 ± 1% and 0.7 ± 0.3% in the absence and presence of ST2262 ($P<0.01$), respectively. Since ST2262 has a relatively low affinity for rodent and guinea pig $Na_V1.7$, we limited our studies to GN8493 in guinea pigs. GN8493 abolished the $Na_V1.7$ responses in the airway parasympathetic nerves with a -log (M) IC_{50} of 5.8 ± 0.2 (n=6). The sympathetic contraction of the isolated abdominal aorta was similarly blocked with a -log (M) IC_{50} of 6.4 ± 0.3. Single neuron RT-PCR revealed that 11 of 11 neurons isolated from guinea pig stellate ganglia express $Na_V1.7$ mRNA. These data support the hypothesis that pharmacologically blocking $Na_V1.7$ with selective inhibitors is likely to reduce sympathetic tone in certain vascular beds.

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Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.14/C15

Topic: B.03. Ion Channels

Title: $Na_V1.1$ selective potentiators increase pv^+ fast-spiking interneuron excitability, normalize inhibition/excitation imbalance and restore motor performance in a mouse model of dravet syndrome

Authors: *S. THOUTA, M. WALDBROOK, K. BURFORD, C. DUBE, M. SORIANO, R. DEAN, V. LOFSTRAND, H. CLEMENT, S. WESOLOWSKI, J. EMPFIELD, J. GILBERT, J. JOHNSON JR, S. GOODCHILD;
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Abstract: Loss-of-function variants of *SCN1A* cause Dravet Syndrome and generalized epilepsy with febrile seizures plus (GEFS+), by decreasing $Na_v1.1$ expression and function of inhibitory interneurons. The resulting hypo-excitability of interneurons reduces inhibitory input onto excitatory neurons, leading to epilepsy and other co-morbidities. To date, there are no subtype selective potentiators of Nav1.1 channels clinically available that directly address the underlying mechanisms of the disease. We have identified potent, isoform-selective, brain penetrant small molecule potentiators of $Na_V1.1$ channels with good drug-like properties that increase Nav1.1 current and restore the firing activity of parvalbumin-expressing, fast-spiking GABAergic interneurons in Dravet Syndrome mice ($Scn1a^{+/-}$). The firing properties of excitatory neurons were not affected by the compounds. Wild-type interneurons were similarly not affected by the compound. Furthermore, we also show that the compounds normalize the imbalance in spontaneous excitatory and inhibitory synaptic input to pyramidal neurons in $Scn1a^{+/-}$ mice. When tested *in vivo*, these compounds suppress seizures in an $Scn1a^{+/-}$ mouse 6 Hz seizure model and improve motor dysfunction in the rotarod assay. In conclusion, our precision medicine approach, that specifically targets the pathophysiological deficit in Dravet Syndrome, may provide a novel approach to control seizures and to ameliorate other co-morbidities

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Poster

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Program #/Poster #: PSTR251.15/C16

Topic: B.03. Ion Channels

Support: NIH Grant NS113991
NIH Grant NS128543

Title: Targeting the $Na_v1.8$Magi1 interaction with lipidated peptidomimetics attenuate entrapment injury pain behaviors in mice

Authors: *M. MARTIN[1], G. GUERRERO[2], A. BHATTACHARJEE[3];
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Abstract: Entrapment neuropathies occur when the nerve becomes compressed between other structures in the body and are the most common type of neuropathic pain. Previous studies have

shown that in preclinical models of entrapment injuries there is an increase in $Na_V1.8$ trafficking and insertion in the membrane. This increase in $Na_V1.8$ channel activity is believed to underly neuropathic pain. Our lab previously identified the WW domain-containing scaffold protein called Magi1 as the putative scaffold protein responsible for $Na_V1.8$ stabilization in the nociceptor membrane (PMID: 30860870). Using the sciatic nerve cuff model of entrapment injury in male and female mice, we used both a genetic approach and a pharmacological approach to investigate the role of the Magi1-$Na_V1.8$ interaction in neuropathic pain. The Hargreaves thermal, von Frey fiber mechanical, and dynamic weight-bearing sensitivity assays were used to confirm and monitor neuropathic pain. After Magi1 was genetically knocked down unilaterally in the sciatic nerve, we found that there was an increase in the thermal withdrawal latency in neuropathic mice compared to the scrambled shRNA-treated mice. We also saw an increase in the percent weight borne on the ipsilateral paw in the Magi-1 knockdown mice compared to scrambled shRNA-treated mice. For von Frey sensitivity, there was an increase in the withdrawal threshold of the Magi1 knockdown mice. We noted sex differences in response to the Magi1 knockdown. In a parallel set of experiments, we injected a lipidated $Na_V1.8$ WW domain peptidomimetic into the ipsilateral paw. We found in an increase in thermal withdrawal latency in the peptide treated mice compared to the scrambled peptide treated mice that lasted for >21 days. There was also a similar increase in the paw withdrawal threshold in von Frey sensitivity. We also saw a change in the percent weight borne on the ipsilateral paw in the NaV1.8 WW peptide treated mice compared to scrambled control. Pharmacologically targeting the $Na_V1.8$ interaction with Magi1 is analgesic in mice undergoing nerve entrapment neuropathic injury. Future studies will look at the effect this peptidomimetic has on other chronic pain models.

Disclosures: **M. Martin:** None. **G. Guerrero:** None. **A. Bhattacharjee:** None.

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR251.16/C17

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Support: ANR-21-CE18-0042 Nav1.2RESCUE - France
ANR-11-LABX-0015-01 LabEx ICST - France
Foundation Jérôme Lejeune - France
ANR-15-IDEX-01 UCA-Jedi - France

Title: Negative dominance, a specific pathological mechanism of autism spectrum disorder SCN2A/$Na_V1.2$ sodium channel variants.

Authors: S. CESTELE[1], S. DHIFALLAH[1], C. BIANCHINI[2], D. MEI[2], N. LEROUDIER[1], S. BALESTRINI[2,3], R. GUERRINI[2,3], ***M. MANTEGAZZA**[1,4];
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Antipolis, France; [2]Dept. of Neuroscience, A.Meyer Children's Hosp., Pediatric Neurol. and Neurogenetics Unit and Labs., Florence, Italy; [3]Univ. of Florence, Florence, Italy; [4]Inserm, Valbonne - Sophia Antipolis, France

Abstract: Pathogenic variants of the *SCN2A* gene, coding for the $Na_V1.2$ voltage gated sodium channel alpha subunit, can cause a wide phenotypic spectrum, including mild epilepsy, different types of developmental and epileptic encephalopathies (DEEs) or different types of neurodevelopmental disorders without epilepsy. Functional studies have shown that variants implicated in infantile-childhood onset DEEs or neurodevelopmental disorders cause loss of function (LoF), but the genotype-phenotype relationships within these variants are not clear yet. We have investigated functional effects of 14 of these variants (7 of them not yet published) in transfected cell lines and neurons in primary culture, either expressing the mutant in isolation or co-expressing mutant and wild-type $Na_V1.2$, to reproduce the conditions of heterozygosis. We observed that all the mutants show LoF when expressed in isolation, either because of reduced current density or because of modifications of gating properties. Notably, when co-expressed with the WT, mutants causing autism spectrum disorder (ASD) without epilepsy induced negative dominance by reducing the current density of the WT and leading overall to more than 50% reduction in current density. Differently, those causing schizophrenia or DEEs did not show negative dominance. Mutagenesis experiments showed that the negative dominant effect of the ASD mutants depends on regions in the channel protein that have been implicated in the interaction of two Na^+ channel alpha-subunits. Moreover, radioactive binding experiments in cell lines and STED super-resolution microscopy experiments in neurons showed that ASD mutants are not targeted to the plasma membrane.Thus, we have disclosed a novel specific pathological mechanism for *SCN2A*/$Na_V1.2$ variants involved in ASD without epilepsy. Our results are consistent with a mechanism in which ASD mutant alpha subunits, interacting with the WT alpha subunit, reduce the targeting of the alpha subunit dimers to the plasma membrane.

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Poster

PSTR251. Sodium Channels

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Topic: B.03. Ion Channels

Support: Agence Nationale de la Recherche: ANR-21-CE18-0042 - Nav12RESCUE; Labex Ion Channels Science and Therapeutics: program number ANR-11-LABX-0015.

Title: An optical analysis of the Na^+ influx, of the Ca^{2+} influx and of the action potential shape in the axon initial segment of neocortical pyramidal neurons in a $Na_V1.2$ knock-out mouse

Authors: *F. ABBAS[1], L. BLÖMER[1], M. SIMONTI[2], S. CELESTE[2], M. MANTEGAZZA[2], M. CANEPARI[1];
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Abstract: ***An optical analysis of the Na^+ influx, of the Ca^{2+} influx and of the action potential shape in the axon initial segment of neocortical pyramidal neurons in a $Na_v1.2$ knock-out mouse*** **Fatima Abbas**, **Laila Ananda Blömer**, **Martina Simonti**, **Sandrine Cestele**, **Massimo Mantegazza**, **Marco Canepari**The voltage-gated Na^+ channel (VGNC) $Na_v1.2$ is one of the two Na^+ channels expressed in the axon initial segment (AIS) of pyramidal neurons, responsible for the generation of the action potential (AP). Several neuronal disorders are associated with constitutive spontaneous mutations of the *SCN2A* gene leading to loss of function of the $Na_v1.2$ VGNC. Thus, heterozygote $Na_v1.2$ knock-out (*Scn2a*$^{+/-}$) mice are considered animal models to investigate the physiological changes associated with these channelopathies. Here we present the results of an analysis of AIS Na^+ and Ca^{2+} influx, as well as AIS APs, in layer-5 neocortical pyramidal neurons of a *Scn2a*$^{+/-}$ mouse. The analysis, performed using ultrafast imaging techniques (50-100 µs time resolution), was carried out in brain slices prepared from mice during the third and fourth postnatal week, when the *Scn2a*$^{+/-}$ mouse displays autistic-like phenotype associated with impaired memory and reduced reactivity to stressful stimuli [1]. The Na^+ influx in the proximal part of the AIS was slightly smaller in *Scn2a*$^{+/-}$ mice with respect to wild-type (*Scn2a*$^{+/+}$) mice. Since we recently reported that $Na_v1.2$ VGNCs also mediate a Ca^{2+} current that shapes the generating AP [2], we also performed a comparative analysis of Ca^{2+} current and AP waveform in *Scn2A*$^{+/-}$ and *Scn2a*$^{+/+}$ mice to investigate whether the $Na_v1.2$ loss of function can lead to a change in the AP shaping during its generation. As we also found a slight decrease of $Na_v1.2$ Ca^{2+} influx in *Scn2a*$^{+/-}$ mice, we conclude that this analysis can be considered as a first step to correlate the behavioral dysfunction with the cellular event of AP generation, also opening the gate to future utilizations of the technique for therapeutic assessments. [1] Léna I, Mantegazza M (2019) Sci Rep 9:12886. doi: 10.1038/s41598-019-49392-7.[2] Filipis L, Blömer LA et al. (2023) J Physiol 601:1957-1979. doi: 10.1113/JP283801.

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Poster

PSTR251. Sodium Channels

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Topic: B.03. Ion Channels

Support: ANR-21-CE18-0042 Nav1.2RESCUE - France
ANR-11-LABX-0015-01 LabEx ICST - France
Foundation Jérôme Lejeune - France
ANR-15-IDEX-01 UCA-Jedi - France

Title: A new mouse model of non-syndromic autism spectrum disorder carrying the human negative-dominant mutation L1314P of the SCN2A/$Na_v1.2$ sodium channel

Authors: *M. SIMONTI[1], S. CESTÈLE[1], F. DUPRAT[1], I. LÉNA[1], M. MANTEGAZZA[1,2]; [1]Inst. of Mol. and Cell. Pharmacol. (IPMC), Univ. Cote d'Azur, CNRS, Valbonne - Sophia Antipolis, France; [2]Inserm, Valbonne - Sophia Antipolis, France

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficits, impaired social behaviour and stereotypies. Genetic variants in the *SCN2A* gene (encoding the voltage-gated sodium channel $Na_v1.2$) cause different neurodevelopmental diseases with or without epilepsy, and are among those with the strongest association with ASD. Functional studies that we performed co-expressing mutants and wild type $Na_v1.2$ in transfected cells to mimic heterozygosis have shown that variants causing ASD without epilepsy (non-syndromic) selectively induce negative dominance, leading to an overall >50% reduction of $Na_v1.2$ function. We generated a novel heterozygous knock-in mouse carrying one of these mutations that cause negative dominance and ASD, L1314P. We characterized behavioural features of these mice through a battery of tests at young (P23-44) and adult (>P70) age. *Scn2a*$^{L1314P/+}$ young male mice present some stereotyped repetitive behaviours and cognitive deficits in risk-assessment and decision-making processes, recapitulating some of the main symptoms observed in ASD patients. To determine the neuronal mechanism that generates these features, we performed whole-cell patch-clamp recordings in brain slices obtained from pups (postnatal day, P5-9) and young mice (P25-30). We evaluated potential impairments in layer 5 pyramidal neurons (PYRs) of the medial prefrontal cortex caused by the mutation in heterozygous *Scn2a*$^{L1314P/+}$ mice. Our results show that immature *Scn2a*$^{L1314P/+}$ PYRs are hypoexcitable, with reduced action potential amplitude and velocity, but without any differences in the voltage threshold. Thus, our novel mouse model is a relevant ASD model. It can be used to shed light on pathological mechanisms that are specific to ASD and to develop new targeted therapeutic strategies.

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Poster

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Topic: B.03. Ion Channels

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PCCR Grant P30CA023168
Walther Cancer Foundation
PIDD
PIIN

Title: Modeling disease phenotypes of autism-associated voltage-gated sodium channel Nav1.2 mutations using advanced human brain assembloids

Authors: *X. CHEN, J. ZHANG, K. WETTSCHURACK, M. I. OLIVERO ACOSTA, M. EATON, M. WANG, E. N. CREAGER, M. S. HALURKAR, Z. QUE, B. DEMING, J. WU, Y. ZHAO, Y.-E. YOO, Y. YANG;
Medicinal Chem. and Mol. Pharmacol., Purdue Univ., West Lafayette, IN

Abstract: The utilization of three-dimensional (3D) human brain organoids for the investigation of neurological disorders has experienced a remarkable surge in recent years. Organoids, derived from human induced pluripotent stem cells (hiPSCs), are widely recognized as a promising model for studying human neurodevelopmental disorders and developing new treatments for clinical translation. One notable gene implicated in neurodevelopmental disorders, such as autism and epilepsy, is *SCN2A*, which encodes the voltage-gated sodium channel Nav1.2 mediating neuronal action potential firing in the brain. Mutations in this *SCN2A* gene give rise to dysfunction in the Nav1.2 channel. Notably, various mutations in this gene can lead to intricate alterations in neuronal excitabilities, sometimes even resulting in contrasting phenotypes. *SCN2A*-C959X, known as a protein-truncating/loss-of-function (LoF) mutation, has been identified in children with severe autism but with no disease-modifying treatment exists. Therefore, it is imperative to determine how the *SCN2A*-C959X mutation impacts neural activity, with the ultimate goal of mitigating these *SCN2A*-associated impairments. To gain a better understanding of how *SCN2A*-C959X contributes to circuit dysfunction and impairments, we are constructing an advanced *in vitro* 3D human organoid model known as "assembloids" to partially recapitulate the key circuits in the human brain. By using assembloids, we are conducting molecular, imaging, and electrophysiological studies to elucidate how Nav1.2 deficiency renders disease phenotypes at both the single neuron and cross-brain region circuitry levels. In summary, with this current study focusing on a typical *SCN2A* protein-truncating mutation, specifically *SCN2A-C959X*, our innovative approach employing assembloids composed of 3D human brain organoids and connecting circuitry offers a promising avenue to explore the impact of *SCN2A* LoF mutations on neuronal function and circuit impairments. We aim to unravel the underlying mechanisms of Nav1.2 deficiency-related diseases to help develop novel therapeutic strategies.

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Poster

PSTR251. Sodium Channels

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.20/C21

Topic: B.03. Ion Channels

Support: Fondecyt 1220680

Title: Role of I_h current in the intrinsic excitability of auditory cortex of fmrp knockout mice

Authors: *C. MORENO, D. RIQUELME, C. CEA, E. LEIVA;
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Abstract: Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by an increase in the CGG codon repeats (over 200 repeats) in the promoter of the fmr1 gene, that leads to a silencing of the gene and a loss of expression of the Fragile X Mental Retardation Protein (FMRP). FXS patients presents auditory hypersensitivity caused by a decrease in the excitability of neurons in layer 2/3 and 5 in the auditory cortex due to an increase in the excitability of the neurons downstream the auditory cortex, altering the auditory processing of external stimuli. In this regard, it has been described that in FMRP KO mice, the I_h current, composed by the HCN channels, is decreased. The I_h current is critical to modulate excitability, synaptic integration and filter capabilities in the neurons; in this context, we investigated the role of I_h current in the homeostatic regulation of the intrinsic excitability of pyramidal neurons in the layer 2/3 and 5 of the auditory cortex. In this work, using a combination of patch-clamp and immunofluorescence, we found that neurons in the auditory cortex of Fmr1KO mice have an increased synaptic activity with a decreased action potential firing frequency, a hyperpolarized resting membrane potential and a decreased membrane resistance and sag, suggesting a homeostatic compensation through a decrease in intrinsic excitability. Additionally, we found a decreased HCN1 expression in layer 1 of the auditory cortex; however, the inhibition of the I_h current with ZD7288 did not reverse the changes observed in the firing frequency, nor other parameters related to the intrinsic excitability. These results show that not only I_h current participates in the homeostatic plasticity of Fmr1KO mice, but other conductances may contribute to this phenotype. This study shed light on the mechanism of homeostatic compensation through changes in ion channel activity, its expression and how it contributes to the altered neuronal processing in FXS.

Disclosures: C. Moreno: None. **D. Riquelme:** A. Employment/Salary (full or part-time):; University of Santiago de Chile. **C. Cea:** A. Employment/Salary (full or part-time):; University of Santiago de Chile. **E. Leiva:** A. Employment/Salary (full or part-time):; University of Santiago de Chile.

Poster

PSTR251. Sodium Channels

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Program #/Poster #: PSTR251.21/C22

Topic: B.03. Ion Channels

Support: NIH Grant R01NS117585
NIH Grant R01NS123154

Title: Evaluation of tetracycline-controlled overexpression of human K_V1.1 to alleviate disease phenotypes in Na_V1.2-deficient mice

Authors: *B. DEMING[1], J. ZHANG[2], M. HALURKAR[2], E. PEREZ-REYES[3], Y. YANG[2]; [1]Purdue Univ., west lafayette, IN; [2]Medicinal Chem. and Mol. Pharmacol., Purdue Univ., West Lafayette, IN; [3]Univ. of Virginia, Charlottesville, VA

Abstract: The CDC estimates that 1 in 36 children have ASD in the United States. A major characterization of ASD is social abnormalities. Genetic variants in *SCN2A*, a gene encoding the voltage-gated sodium channel Na_V1.2, have been identified as a leading monogenic cause of ASD; however, there are few FDA-approved drugs to aid with the social impairments seen in *SCN2A*-deficiency-related ASD patients. We have established a *Scn2a* deficient mouse model, which displays social deficits and neuronal hyperexcitability. We identified that this mouse model has a significant downregulation of multiple voltage-gated potassium channels (K_V), especially K_V1.1, in the brain. We further showed that the application of 4TFMPG, a K_V1.1 channel opener, corrects the hyperexcitability in neurons of Na_V1.2-deficient mice, further supporting a key role of K_V1.1 in mediating the disease phenotypes. However, even though 4TFMPG showed promise in rescuing the neuronal phenotypes *ex vivo*, it is a tool compound. Thus its bioavailability and *in vivo* safety are unknown. With growing FDA approval, Adeno-Associated Viruses (AAVs) based gene therapies to deliver a genetic payload to neurons are booming. In particular, an AAV with a Tet-on system driving expression of human K_V1.1 has recently been developed for potential clinical trial use by Dr. Perez-Reyes at UVA. Originally designed to treat seizures, this system utilizes a reverse Tetracycline-controlled transcriptional activator to drive the expression of *KCNA1* to produce exogenous Kv1.1 in the presence of a tetracycline, such as doxycycline. In this study, we tested whether the tetracycline-controlled overexpression of human K_V1.1 could rescue behavioral and neuronal phenotypes in Na_V1.2-deficient mice. Our preliminary results suggest that the overexpression of K_V1.1 in Na_V1.2-deficient mice alleviates the social deficits. Furthermore, we are examining the neuronal excitability in *Scn2a*-deficient mice transduced with AAV-K_V1.1. We anticipate our study would expand the utility of Kv1.1-based gene therapy to potentially alleviate disease phenotypes seen in *SCN2A*-related ASD.

Disclosures: B. Deming: None. **J. Zhang:** None. **M. Halurkar:** None. **E. Perez-Reyes:** None. **Y. Yang:** None.

Poster

PSTR251. Sodium Channels

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Topic: B.03. Ion Channels

Support: R01 NS117585
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Fulbright-Colciencias Scholarship Program
Indiana Clinical and Translational Sciences Institute
Purdue University Institute for Drug Discovery
Purdue Institute for Integrative Neuroscience
FamilieSCN2A Foundation Action Potential Award
FamilieSCN2A Foundation Hodgkin-Huxley Award

Title: Modeling epilepsy-related SCN2A variant L1342P with CRISPR/Cas9-edited human-induced pluripotent stem cell-derived cortical spheroids

Authors: *M. OLIVERO ACOSTA[1], Z. QUE[2], M. WANG[3], J. ZHANG[2], C. OTTERBACHER[3], X. CHEN[2], T. NGUYEN[4], B. DEMING[5], K. WETTSCHURACK[4], J. WU[6], Y. YANG[2];
[1]Purdue Univ., west lafayette, IN; [2]Purdue Univ., [3]Purdue Univ., West Lafayette, IN; [4]Purdue Univ., Purdue Univ., Lafayette, IN; [5]Purdue Univ., Purdue Univ., west lafayette, IN; [6]Prudue Univ., Prudue Univ., West Lafayette, IN

Abstract: Recent developments in stem cell technology have provided new avenues for studying neurological disorders via the generation of human neuron-based models, aiming to explore disease mechanisms and test for interventions. The SCN2A gene encodes for voltage-gated sodium channel Nav1.2, a protein that mediates action potential firing. SCN2A pathogenic mutations have been associated with epilepsy. An example is L1342P, identified in several patients with severe seizures that are hard to treat with current medications (Que, Olivero-Acosta et al., 2021). Given that no disease-modifying treatment exists, there is an urgent need to generate novel tools to probe at the variant-specific disease mechanisms and screen for efficient therapies. In our recent work, we have demonstrated that hiPSC-derived 2D- neuronal monolayers carrying the CRISPR/Cas9-edited L1342P-mutant channel display hyperexcitability (Que, Olivero-Acosta et al., 2021). However, the L1342P variant's impact on neurodevelopment in the more physiologically relevant 3D models, such as cortical spheroids, remains unknown. Human cortical spheroids are 3D aggregates that resemble the human cortex. This model is characterized by a neuroectoderm-like epithelium that matures over time, spawning cortical neurons that arrange themselves in patterns observed in the postnatal brain (Sloan et al., 2018). They are composed mainly of glutamatergic neurons (Yoon et al., 2019), and when mature, they display robust electrical activity. In the present study, we describe the use of CRISPR/Cas9-edited hiPSCs to generate cortical spheroids carrying the epilepsy-related SCN2A-L1342P variant to study its effect on neuron development and other disease phenotypes. Techniques used include advanced microscopy imaging, patch-clamp, and microelectrode array (MEA) recordings. Our results will provide insight into how disease-causing Nav1.2 genetic variants may affect neuronal excitability and development, as well as establish a cutting-edge 3D cortical spheroid platform suitable for testing novel interventions.

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Poster

PSTR251. Sodium Channels

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Program #/Poster #: PSTR251.23/C24

Topic: B.03. Ion Channels

Support: FONDECYT 1220680

Title: Cholinergic transmission modulates TRPM4 channel trafficking in cortical neurons

Authors: ***P. LEYTON**[1], D. RIQUELME[2], E. LEIVA-SALCEDO[2];
[1]Biol., [2]Dept. of Biol., Univ. of Santiago of Chile, Santiago, Chile

Abstract: Neuronal excitability is determined by the type, density, and localization of ion channels, transporters, and receptors in the neuronal plasma membrane. One regulator of excitability is cholinergic transmission, working directly on channels or through second messengers. Recently we found that TRPM4 is activated by cholinergic stimulation, through Gq-coupled M1, M3, and M5 muscarinic receptors, which increases neuronal excitability. TRPM4 is a non-selective, Ca^{2+} activated, and monovalent cation permeant channel which is expressed in several brain regions such as prefrontal cortex, CA1 hippocampus, olfactory neurons among others. In pyramidal neurons it presents a somatodendritic expression with an intense perinuclear signal, which strongly suggests its presence in intracellular compartments. In this work, we explore the mechanism by which TRPM4 increases neural excitability after cholinergic stimulation by investigating the change in the trafficking of these ion channels. Using a combination of immunofluorescence, confocal microscopy, and fluorescent recovery after photobleaching (FRAP) assay, we investigated the localization of TRPM4 in mice cortical neuron cultures on four regions: plasma membrane, early endosome, Golgi apparatus, and endoplasmic reticulum and found that cholinergic stimulus increases TRPM4 levels in Golgi and plasma membrane. Moreover, we found in FRAP assay that cholinergic stimulation decreases the time constant of TRPM4 translocation to the plasmatic membrane suggesting an increase in the incorporation of channels to the membrane. Together, these results shed light on the mechanism of cholinergic modulation of neuronal excitability through the regulation of TRPM4 trafficking.

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Poster

PSTR251. Sodium Channels

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FamilieSCN2A foundation for the Action Potential Grant
Indiana Spinal Cord & Brain Injury Research Fund
Indiana CTSI funded, in part by UL1TR002529

Title: Microglial over-pruning of synapses during development in autism-associated SCN2A-deficient mice and human cerebral organoids

Authors: *J. WU[1], J. ZHANG[2], Y.-E. YOO[2], Z. QUE[2], K. WETTSCHURACK[2], B. DEMING[2], N. CUI[2], M. I. OLIVERO ACOSTA[2], M. HALURKAR[2], Y. YANG[2];
[1]Prudue Univ., West Lafayette, IN; [2]Purdue Univ., West Lafayette, IN

Abstract: Microglia play a pivotal role in regulating synaptic remodeling. Studies have demonstrated that microglia are capable of modulating synapses, performing crucial functions such as pruning excessive spines in normal development and neurological disorders like autism and schizophrenia. Recent large-scale human genetic studies have demonstrated mutations in the *SCN2A* gene as the leading cause of monogenic autism. SCN2A encodes voltage-gated sodium channel Nav1.2, expressed in the central nervous system mediating action potential initiation, propagation, and backpropagation. The majority of these *SCN2A* mutations identified in children with autism are either loss-of-function or protein-truncating, collectively referred to as *SCN2A* deficiency. Our recent studies found that Nav1.2-deficient mice displayed severely impaired learning and memory. We further demonstrated that hippocampal neurons have reduced spine density, and microglia engulfed excessive post-synapses throughout development and into adulthood in the hippocampal region of Nav1.2-deficient mice. Treatment with PLX3397, which is CSF1R specific inhibitor used to ablate microglia, has been shown to result in about 95% elimination of microglia brain-wide. Moreover, we observed that the dendritic spine density and miniature excitatory postsynaptic currents (mEPSC) of Nav1.2-deficient neurons can be rescued toward the WT level by PLX3397. To extend our findings from rodents to human cells, we established a human cortical organoid model carrying an *SCN2A* protein-truncating mutation C959X identified in children with profound autism. We found that human microglia display increased elimination of post-synapse in cortical organoids carrying the *SCN2A*-C959X genetic mutation. Our research has established the crucial role of microglia in autism-associated models across multiple species, ranging from mice to human cells.

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Poster

PSTR251. Sodium Channels

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Title: Single-cell level transcriptomic analysis to unravel the molecular underpinning in Scn2a-deficient mice

Authors: *Y.-E. YOO[1], J. ZHANG[1], X. CHEN[1], M. EATON[1], H. GAO[3], N. LANMAN[2], Y. YANG[1];
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Abstract: The loss-of-function mutations in the *SCN2A* gene, which encodes a sodium channel critical for action potential initiation and propagation, have been implicated in neurodevelopmental disorders including autism spectrum disorder (ASD) and epilepsy. We established a preclinical mouse model to investigate the impact of *Scn2a*-deficiency and demonstrated that *Scn2a*-deficient mice exhibit major disease phenotypes. However, the cellular heterogeneity within the brain and molecular alteration underlying these phenotypes at a single-cell resolution has not been thoroughly explored. In this study, we conducted single nucleus RNA sequencing (snRNA-seq) on the medial prefrontal cortex (mPFC) of wild-type (WT) and homozygous *Scn2a*-deficient (HOM) mice to examine the effects of *Scn2a*-deficiency on gene expression and the composition of different cell populations. The mPFC brain region was chosen due to its role as a critical hub for social behavior and higher cognitive functions in ASD. Our preliminary analysis revealed differential proportions of cell types in the mPFC between WT and HOM groups. Further analysis of differential gene expression is ongoing to identify cell-type-specific gene expression differences. Together, our findings will reveal gene expression profiles and differential proportions of cell types in the mPFC region of *Scn2a*-deficient mice, advancing our understanding of the underlying pathology of disease phenotypes due to *Scn2a*-deficiency. We anticipate that these findings could serve as a foundation for the development of novel therapeutic interventions toward new molecular targets in a cell-type-specific manner.

Disclosures: Y. Yoo: None. **J. Zhang:** None. **X. Chen:** None. **M. Eaton:** None. **H. Gao:** None. **N. Lanman:** None. **Y. Yang:** None.

Poster

PSTR251. Sodium Channels

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR251.26/C27

Topic: B.03. Ion Channels

Support: FamilieSCN2A foundation Hodgkin-Huxley Award

Title: Splicing and phenotypic consequences of SCN2A splice-site genetic variant identified from a child with autism

Authors: K. WETTSCHURACK[1], ***M. S. HALURKAR**[1], M. I. OLIVERO ACOSTA[1], N. LANMAN[2], W. SKARNES[3], Y. YANG[1];
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Abstract: *SCN2A* encodes the alpha subunit of the voltage-gated sodium channel Nav1.2, which is essential for proper neuronal function. Mutations in *SCN2A* have been associated with a range of neurodevelopmental disorders, including autism spectrum disorder and epilepsy. In this study, we aimed to investigate a specific splice-site variation (SCN2A c.3973-1GtoA) using induced pluripotent stem cells (iPSCs). The c.3973-1GtoA variation was recently identified from a child with autism spectrum disorder (ASD). This variation occurs in the conserved splice site before Exon 22. While it is suspected that mutations in a highly conserved splice site will affect the splicing and assembling of exons in the mRNA, how exactly c.3973-1GtoA affects the splicing and function of Nav1.2 to alter neuronal activity is unknown. We have used CRISPR/Cas9 editing techniques to engineer the c.3973-1GtoA variation into a reference iPSC cell line, of which a GCaMP6 biosensor was engineered in the AAVS1 safe harbor. We then differentiated these engineered iPSCs into cortical neurons that are known to express Nav1.2. Using mRNA/cDNA extracted from the differentiated cells, our preliminary data suggest that c.3973-1GtoA variation leads to a shortened *SCN2A* mRNA. The analysis of the neuronal activity in neurons carrying c.3973-1GtoA is ongoing using a GCaMP6-based Calcium signal biosensor. Our results will shed light on the transcriptional and phenotypic changes in neurons by the c.3973-1GtoA variation, allowing us to identify key disease phenotypes for testing personalized therapeutic interventions.

Disclosures: K. Wettschurack: None. **M.S. Halurkar:** None. **M.I. Olivero Acosta:** None. **N. Lanman:** None. **W. Skarnes:** None. **Y. Yang:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.01/C28

Topic: B.09. Glial Mechanisms

Support: R21DA052447

Title: Effects of cocaine self-administration on nucleus accumbens core astrocyte calcium dynamics

Authors: *E. V. HARDER[1], J. W. VANRYZIN[2], S. O. AHAOTU-SIMELANE[2], K. J. REISSNER[1];
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Abstract: Psychostimulant use disorders are a major public health concern within the United States. Recent evidence suggests that astrocytes are significantly implicated in cocaine-related changes in the brain underlying relapse and drug dependence. Previously, we found astrocytes in the nucleus accumbens (NAc) core are profoundly structurally impaired following long-access (LgA, 6 h/day, 10 days) cocaine self-administration and 45 days of forced abstinence, as evidenced by a ~40% reduction in surface area, volume, and synaptic colocalization. Considering that astrocytes are positioned to sense neuronal activity at the synapse and accordingly respond by modulating synaptic function, surprisingly little is known about how cocaine-mediated changes can affect astrocyte function and therefore, their ability to regulate synaptic transmission. We hypothesize that cocaine self-administration results in decreased NAc astrocyte responsiveness to input from prelimbic cortex glutamatergic afferents. To test this hypothesis, we used a combination of DREADD-mediated synaptic transmission and GCaMP8s astrocyte calcium imaging in acute brain slices. AAV5-GfaABC1D-GCaMP8s provides 90+% specific expression in rat astrocytes. Using this indicator, we found in acute slices from drug-naïve animals that stimulation of prelimbic to NAc core projections by 1 mM CNO significantly changes astrocyte calcium event frequency in the NAc core, and that the directionality of this change depended upon whether regions of interest (ROIs) were tracked across baseline and 1 mM CNO conditions or whether ROIs were selected independently in each condition based on activity. Further, we find that cocaine self-administration and abstinence results in NAc core astrocyte calcium event frequency that is significantly reduced at baseline but significantly increased during prelimbic to NAc core stimulation, when selecting ROIs independently based on activity. These changes in astrocyte calcium activity may have important implications for astrocyte ability to regulate synaptic function following a history of cocaine. Ongoing work aims to delineate the neurotransmitter systems responsible for these effects and downstream consequences on synaptic transmission. These results provide insights into how functional changes in astrocytes may underlie relapse behaviors.

Disclosures: E.V. Harder: None. **J.W. Vanryzin:** None. **S.O. Ahaotu-Simelane:** None. **K.J. Reissner:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.02/C29

Topic: B.09. Glial Mechanisms

Support: Foerster Bernstein Women In STEM Postdoctoral Fellowship
Chan Zuckerberg Initiative, Neurodegeneration Challenge Network Collaborative grant (2018-191999 and DAF2021-237435)
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National Institute on Aging (P30AG19610 and P30AG072980, Arizona Alzheimer's Disease Center)
Arizona Biomedical Research Commission contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium

Title: Astrocytic LRRK2 Controls Astrocyte Morphology and Synaptic Connectivity

Authors: *S. WANG[1], D. SIVADASAN BINDU[1], C. TAN[1], K. SAKERS[1], T. TAKANO[2], M. RODRIGUEZ[1], K. DIMOND[1], S. H. SODERLING[1], A. R. LA SPADA[3], C. EROGLU[1];
[1]Cell Biol., Duke Univ., Durham, NC; [2]Neurophysiol., Keio Univ. Sch. of Med., Japan, Japan; [3]Pathology & Lab. Medicine, Neurology, Biol. Chem., Univ. of California, Irvine, Irvine, CA

Abstract: Astrocytes tightly control neuronal connectivity and function in the brain through direct contact with synapses. These glial cells become reactive during disease pathogenesis, including Parkinson's disease (PD). However, it remains unknown if astrocyte dysfunction is an initiating factor of PD pathogenesis and whether astrocytes can be targeted to stop or reverse the synaptic dysfunction seen in PD. Using *in vitro* and *in vivo* methods, we found that the PD-linked gene Lrrk2 controls astrocyte morphology via regulating the phosphorylation of ERM proteins (Ezrin, Radixin, and Moesin), a structural component of the perisynaptic astrocyte processes. ERM phosphorylation is robustly elevated in mice and humans carrying the LRRK2 G2019S Parkinsonism mutation. Importantly, the reduction of the ERM phosphorylation, specifically in the LRRK2 G2019S in adult astrocytes, is sufficient to restore excitatory synapse number and function deficits in the LRRK2 G2019S knock-in mouse cortex. These results show a role for Lrrk2 in controlling astrocyte morphogenesis and synaptogenic function and reveal that early astrocyte dysfunction in PD could be causal to disruptions in cortical excitatory synaptic connectivity. The astrocytic dysfunction can be corrected by dampening ERM phosphorylation, pinpointing astrocytes as critical cellular targets for PD therapeutics.

Disclosures: S. Wang: None. **D. Sivadasan Bindu:** None. **C. Tan:** None. **K. Sakers:** None. **T. Takano:** None. **M. Rodriguez:** None. **K. Dimond:** None. **S.H. Soderling:** None. **A.R. La Spada:** None. **C. Eroglu:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.03/C30

Topic: B.09. Glial Mechanisms

Support: Brain Canada Foundation 2019 Future Leaders in Canadian Brain Research
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Natural Sciences and Engineering Research Council of Canada (scholarships)
Canada First Research Excellence Fund
Healthy Brain Healthy Lives
RQSHA (FRQS)

Title: Astrocytic cannabinoid receptor 1 promotes resilience by dampening stress-induced blood-brain barrier alterations

Authors: K. DUDEK[1], S. E. J. PATON[1], A. COLLIGNON[1], M. LEBEL[1], O. LAVOIE[1], J. BOUCHARD[1], F. NEUTZLING KAUFMANN[1], L. DION-ALBERT[1], V. CLAVET-FOURNIER[1], L. BANDEIRA BINDER[1], C. MANCA[1], N. FLAMAND[1], M. GUZMAN[2], M. CAMPBELL[3], G. TURECKI[4], N. MECHAWAR[4], F. LAVOIE-CARDINAL[1], C. SILVESTRI[1], V. DI MARZO[1], ***C. MENARD**[1];
[1]Univ. Laval, Quebec City, QC, Canada; [2]Complutense Univ. of Madrid, Madrid, Spain; [3]Trinity Col. Dublin, Dublin, Ireland; [4]McGill Univ., Montreal, QC, Canada

Abstract: Major depressive disorder (MDD) is a leading cause of disabilities worldwide, with one out of five individuals affected throughout their lifetime. Blood-brain barrier (BBB) alterations contribute to stress vulnerability and development of depressive behaviors. In contrast, neurovascular adaptations underlying stress resilience remain unexplored. The BBB is a dynamic frontier responsible for regulation of molecular exchange between the periphery and the brain, critical for the maintenance of its homeostasis. We observed that high expression of astrocytic cannabinoid receptor 1 (CB1, encoded by the *Cnr1* gene) in the nucleus accumbens (NAc) shell, particularly in the endfeet ensheathing blood vessels, is associated with resilience despite chronic social stress exposure. The endocannabinoid system is a crucial regulator of stress responses, and its disruption is associated with depressive behaviors in both clinical and preclinical studies. Perivascular astrocytic CB1 remain understudied despite perfect positioning to modulate BBB properties during stress exposure and in mood disorders. Viral-mediated overexpression of *Cnr1* in astrocytes of the NAc shell has baseline anxiolytic effects and dampened stress-induced anxiety- and depression-like behaviors. It also reduced astrocyte inflammatory response and morphological changes following an immune challenge with the cytokine interleukin-6, linked to stress susceptibility and mood disorders. At the preventive and

therapeutic level, physical exercise and antidepressant treatment increased perivascular astrocytic *Cnr1* in mice. Loss of *CNR1* was confirmed in the NAc astrocytes of individuals with MDD. These findings suggest a role for the astrocytic endocannabinoid system in stress responses and possibly, human depression, via BBB modulation.

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Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.04/C31

Topic: B.09. Glial Mechanisms

Support: DA030359

Title: Uncovering cell-specific mechanisms of adolescent cannabis-induced behaviors: a novel role for astrocytes

Authors: *J.-M. N. FERLAND[1], Y. HURD[2];
[1]Icahn Sch. of Med. at Mount Sinai Friedman Brain Inst., Brooklyn, NY; [2]Icahn Sch. of Med. at Mount Sinai Friedman Brain Inst., New York, NY

Abstract: Cannabis is one of the most popular drugs of abuse worldwide. One unintentional consequence of shifts in attitudes towards cannabis after legalization and decriminalization efforts is a rise in use amongst adolescents, including occasional and frequent use. Despite positive perceptions of cannabis, use during adolescence when the brain is still undergoing significant maturation is associated with increased risk for developing psychopathologies including Cannabis Use Disorder (CUD). Clinical data shows a strong link between regular cannabis use and several behaviors associated with addiction including increased emotional dysregulation, anxiety, and risky decision making. Furthermore, emerging data now indicate that use of high potency products (which now dominate the market) increase the risk of developing CUD. However, the causal relationship between adolescent cannabis exposure, THC potency, and these behavioral outcomes remains highly debated, and the mechanisms underlying THC-induced phenotypes are poorly understood. Using a rat model, we assessed the relationship between adolescent THC exposure and dose on addiction-related behaviors in adulthood. Compared to low dose and control animals, exposure to high dose THC during adolescence significantly increased stress reactivity, risky decision making, and THC-induced cognitive deficits in adulthood---phenotypes linked to CUD. RNA sequencing and immunohistochemistry analyses of the basolateral amygdala, a region critically implicated in stress responsivity and

cognition, revealed that astrocytes were specifically associated with high dose THC-induced stress reactivity, including downregulation of genes that regulate astrocyte glutamate homeostasis, calcium signaling, and astrocyte morphology. Impairments in decision making and impulse control after adult re-exposure to THC also correlated to astrocyte plasticity *Gfap* expression in the basolateral amygdala and prelimbic cortex. These data reveal an emerging role for astrocytes in adolescent THC-induced behaviors. Ongoing studies are examining the relationship between decision making and edible THC consumption, the impact of adolescent THC exposure on these outcomes, and the unique role astrocytes play in cognitive vulnerability to CUD-like phenotypes.

Disclosures: J.N. Ferland: None. **Y. Hurd:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.05

Topic: B.09. Glial Mechanisms

Support: K01DA054339

Title: High-throughput assessment of astrocyte morphology in the ventral striatum reveals striking heterogeneity during heroin withdrawal and relapse.

Authors: *A. KRUYER;
Univ. of Cincinnati, Cincinnati, OH

Abstract: Astrocytes regulate excitatory activity at striatal synapses via gliotransmission, glutamate uptake, and spatial buffering of glutamate spillover. Astrocyte insulation of synapses in the nucleus accumbens is dynamic and circuit-selective after addictive drug use, and astrocyte adjacency to different synaptic subtypes tunes synaptic activity necessary for drug seeking. Given the critical effects of astrocyte structural plasticity on neural circuit activity in the striatum, we developed a high-throughput machine-learning approach to assess astrocyte structural heterogeneity within and across ventral striatal nuclei based on astrocyte expression of the cytoskeletal marker GFAP. This deep-learning framework permits automated detection of GFAP-immunolabeled astroglia despite near-adjacency of densely tiled cells. Next, we applied automated segmentation of individual astrocytes and classified astrocytes according to brain region and drug treatment groups based on consistent and identifiable features. Assessment of astrocyte features across striatal subregions revealed structurally unique astrocyte subpopulations across adjacent portions of the nucleus accumbens that were uniquely altered after withdrawal from heroin use and during seeking. Our approach also indicated that astrocyte network connectivity was significantly reduced across the ventral striatum after chronic heroin use, highlighting important avenues for future research.

Disclosures: A. Kruyer: None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.06/C32

Topic: B.09. Glial Mechanisms

Support: UNC Cowan Research Excellence Award
NIH DA052447

Title: Cocaine induced microglia pruning of astrocytes

Authors: A. TESTEN[1], T. J. BELLINGER[1], J. W. VANRYZIN[1], H. WANG[1], J. P. FRANKLIN[1], M. GASTINGER[2], *K. J. REISSNER[3], ***K. J. REISSNER**[1];
[1]Psychology and Neurosci., UNC, Chapel Hill, NC; [2]Biptplane, USA, Lancaster, PA; [3]UNC-CH, Chapel Hill, NC

Abstract: Accumulating evidence indicates effects of illicit drug use on astrocytes. In particular, both the structure and function of nucleus accumbens (NAc) astrocytes are significantly impaired by rat cocaine self-administration. We recently reported that 10 days of long-access (6h/day) self-administration access followed by 45 days of home cage access results in a ~40% reduction in surface area, volume, and synaptic colocalization of NAc astrocytes (Kim et al., 2022 eNeuro). To evaluate the nature of these observed structural deficits more fully, we developed a novel approach to perform three-dimensional branching complexity analysis of individual astrocytes. This analysis revealed cocaine-dependent reductions in the number of astrocyte branches and segments, with no effect on segment length, suggesting that reductions in morphometric features may be driven by branch loss rather than overall shrinkage of segments. In order to explore whether loss of astrocyte peripheral processes might occur as a consequence of microglia pruning, we analyzed Iba-1 labeled microglia for evidence of astrocyte-derived Lck-GFP inclusions at withdrawal day 45 following cocaine versus saline self-administration. We indeed observed inclusions of fluorescent astrocyte membranes within microglia, which were significantly more prevalent in the cocaine versus the saline group. Further, inclusions were positive for a complement component 3 (C3) protein, suggesting implication of a complement-dependent pathway in pruning. To confirm this, we blocked C3 receptor interactions using neutrophil inhibitory factor (NIF) peptide across abstinence following cocaine self-administration. Administration of intra-NAc NIF peptide significantly impaired behavioral measures of cocaine seeking, and normalized the structure of NAc astrocytes. These results indicate astrocytes as a target of microglia phagocytosis, and indicate microglia-mediated phagocytosis as a contributing mechanism to drug seeking behaviors.

Disclosures: A. Testen: None. **T.J. Bellinger:** None. **J.W. VanRyzin:** None. **H. Wang:** None. **J.P. Franklin:** None. **M. Gastinger:** A. Employment/Salary (full or part-time):; Employee of Bitplane Imaris, Bitplane Imaris. **K.J. Reissner:** None. **K.J. Reissner:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.07/C33

Topic: B.09. Glial Mechanisms

Support: NIH Grant R21 DA052447

Title: Nucleus accumbens astrocytes regulate social behavior in rats

Authors: *J. W. VANRYZIN, K. J. REISSNER;
Dept. of Psychology and Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Appropriate social behavior is necessary for health and survival of many animal species and is often disrupted in psychiatric disorders such as schizophrenia, autism spectrum disorder, and depression. Successful social interactions require not only processing of social information, but also proper integration of social reward. The nucleus accumbens (NAc) is a critical integrative hub in the brain's reward circuitry that has also been shown to be essential for processing social information. Within the NAc, astrocytes are uniquely positioned to sense and regulate a diversity of incoming circuit projections and neurotransmitters. Yet how astrocytes accomplish such a feat and how astrocyte signaling, in turn, affects neuronal circuit activity during social behavior are largely unknown. To this end, we aimed to test the hypothesis that NAc astrocytes dynamically regulate the expression of social behavior in the rat. We first utilized an AAV to overexpress the human plasma membrane calcium-transporting ATPase2 (PMCA2) specifically in NAc astrocytes under the control of the GfaABC1D promoter, to deplete NAc astrocyte Ca2+ signaling. Ca2+ depletion significantly increased the amount of time rats spent interacting with a novel conspecific in an open-cage social test, while also increasing the social preference index in a 3-chamber social preference test. Conversely, activating NAc astrocyte Ca2+ signaling, using an AAV to express the HM3D(Gq) DREADD construct, significantly decreased social interaction time in an open-cage social test when the animals received CNO as compared to saline trials. However, CNO treatment did not affect social preference index in the 3-chamber test. Together, these findings demonstrate that NAc astrocytes can bidirectionally modulate social interaction in the rat via Ca2+. Current studies are underway using fiber photometry with GCaMP8s to measure NAc astrocyte Ca2+ responsiveness to social interaction, in order to characterize the precise nature of the dynamics between NAc astrocyte and neural activity in real-time during social investigation. Collectively, these studies aim to provide novel insight into how social information is processed and integrated with reward circuitry in the brain.

Disclosures: J.W. Vanryzin: None. **K.J. Reissner:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.08/C34

Topic: B.09. Glial Mechanisms

Support: This research was supported by a UKRI Medical Research Council Grant awarded to Professor David Belin

Title: Striatal astrocytic mechanisms underlying the development of compulsive heroin seeking habits

Authors: *T. HYNES[1], M. PUAUD[2], B. J. EVERITT[3], M. FOUYSSAC[2], D. J. BELIN[1]; [2]Psychology, [1]Univ. of Cambridge, Cambridge, United Kingdom; [3]Downing Col., Univ. Cambridge, Cambridge, United Kingdom

Abstract: The development of compulsive heroin seeking is underpinned by a functional coupling of the ventral and the dorsolateral striatum. This coupling has been shown to involve dopaminergic processes, but the cellular and molecular mechanisms they engage have not been fully elucidated. We hypothesised that astrocytes and their striatal syncytium may play a critical role. Astrocytes express dopamine transporter and their syncytium tiles the striatum, thus positioning them well to functionally bridge dopaminergic activity across striatal territories. To investigate this hypothesis, we deployed our novel rodent model of compulsive heroin seeking alongside spatial transcriptomics, virally mediated gene transfer, and classical pharmacology. We first determined the spatiotemporal profile of the functional recruitment of the striatal astrocytic syncytium over the course of the development of compulsive heroin seeking. RNAScope analysis revealed that compulsive heroin seeking was associated with decreased dopamine transporter (DAT) mRNAs in both the anterior dorsolateral striatum (aDLS) and the nucleus accumbens core (NAcC). In contrast, a short-term history of heroin self-administration under continuous reinforcement was associated only with decreased DAT mRNA expression NAcC. Western blots of astrocytes cultured from striatal grafts of individuals had a history of heroin self-administration or a well-established compulsive heroin seeking habit confirmed that the alterations observed in mRNA were also present at the protein level. This pattern of astrocytic DAT regulation suggests that volume-transmitted dopamine could be biased toward the aDLS in the early stages of heroin use, thereby facilitating the transition to compulsive heroin seeking.We next asked whether astrocytes of the NAcC played a causal role in the functional recruitment of the aDLS in dopamine-dependent compulsive heroin seeking. In separate groups of rats, we tested the influence of chronic inhibition (using a virally transduced calcium extruder) or activation (using hM3Dq) of NAcC astrocytes on the functional engagement of the aDLS dopamine-dependent habits following a prolonged history of heroin seeking. This bidirectional modulation of NAcC astrocytes differentially impacted the sensitivity of heroin seeking to bilateral delivery of a dopamine receptor agonist into the aDLS, providing causal evidence for the role of NAcC astrocytes in the development of aDLS-dependent heroin seeking habits.

Disclosures: **T. Hynes:** A. Employment/Salary (full or part-time):; University of Cambridge. **M. Puaud:** None. **B.J. Everitt:** None. **M. Fouyssac:** None. **D.J. Belin:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.09/C35

Topic: B.09. Glial Mechanisms

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Saks Kavanaugh Foundation
Brain & Behavior Research Foundation (Ellen Schapiro & Gerald Axelbaum Investigator) 39864

Title: Striatal astrocytes in dopamine regulation: A new perspective on behavior state transitions and interaction with striosomes.

Authors: *I. LAZARIDIS[1], G. AHN[1], E. HUESKE[1], A. MATSUSHIMA[1], M. SUR[2], A. M. GRAYBIEL[1];
[1]McGovern Inst. for Brain Res., [2]The Picower Inst. for Learning and Memory, MIT, CAMBRIDGE, MA

Abstract: Introduction: The striatum, a core structure in the basal ganglia, plays vital roles in motor control and reward-related learning. Emerging evidence suggests a complex interplay between striatal astrocytes, dopamine, and striosomes within the striatum. Striosomes modulate dopamine regulation by projecting onto dopamine-rich neurons in the substantia nigra pars compacta (SNpc). We hypothesize that astrocytes can potentially affect, either directly through gliotransmitter release or through dopamine regulation, striatal pathway function and can ultimately modulate decision-making behaviors. **Methods:** Our study employed optogenetic stimulation of SNpc dopamine neurons while recording concurrent astrocyte activity. Using two-color photometry imaging, we achieved simultaneous imaging of dopamine release and astrocyte activity in the dorsolateral striatum (DLS) and dorsomedial striatum (DMS) in freely moving mice during a decision-making maze task. Behavioral recordings with DeepLabCut facilitated the labeling and detailed behavioral clustering. We also demonstrated simultaneous imaging of astrocytes and striosomal SPNs at single-cell resolution with a miniaturized endoscope and widefield imaging. **Results:** Astrocyte responses to optogenetically induced dopamine release revealed a strong response of astrocytes to dopamine that mimicked the relationship of endogenous striatal dopamine release and astrocyte activity. Importantly, our simultaneous imaging of astrocytes and dopamine release in freely moving mice revealed a bidirectional interaction. Paired pulse ratio experiments revealed a refractory period in both DLS and DMS astrocytes, but with distinct characteristics. The abolishment of astrocyte response to optogenetically induced dopamine under anesthesia suggests potential indirect effects of dopamine on astrocytes. Finally, we found a correlation between astrocyte activity and task performance, indicating a decrease in astrocyte peak probability during engagement and increased astrocyte calcium activity during behavioral state transitions between task engagement

and free exploration. **Conclusion:** Our findings indicate that striatal astrocytes play an integral role in modulating the dopamine system and suggest potential interaction with striosomal functions. These results underscore the possible influence of astrocytes in modulating dopamine's effects within the dorsal striatum, and their potential involvement in regulating the balance between exploitation and exploration or engagement.

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Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

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Program #/Poster #: PSTR252.10/C36

Topic: B.09. Glial Mechanisms

Support: 1F31DA057113-01A1
NIDA 1R01DA041455
NIDA 1R21DA052447

Title: Using an astrocyte-specific RiboTag AAV to investigate cocaine-mediated effects on nucleus accumbens astrocyte gene expression

Authors: *J. P. FRANKLIN[1], K. J. REISSNER[2];
[1]Neurosci. Ctr., [2]Psychology and Neurosci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Substance abuse continues to be a national public health issue, as substance-related overdose deaths have increased over time. Particularly, there were approximately 1.4 million individuals who were diagnosed with cocaine use disorder (CUD) in 2021 and roughly a 72% increase in cocaine-related overdose deaths from 2014 to 2020. However, an FDA-approved treatment for CUD is lacking. Hence, it is of great importance to investigate mechanisms of CUD and relapse. Historically, neurons have been central to studies on mechanisms of drug abuse, with limited emphasis on the role of glial cells. However, accumulating studies reveal dysregulated glial cell function is associated with substance abuse. We recently reported that astrocytes within the nucleus accumbens (NAc) are significantly (~40%) decreased in surface area, volume, and synaptic colocalization after long-access self-administration of cocaine (6hr/day) followed by protracted abstinence (45d) (Kim et al., eNeuro 2022). However, the underlying mechanisms for these structural changes in NAc astrocytes are unknown. My research utilizes an unbiased transcriptomic approach to identify differentially expressed genes in NAc astrocytes following cocaine self-administration and prolonged abstinence. We hypothesize that cocaine alters expression of astrocyte genes, which mediates the observed decreased NAc astrocytic phenotype and contributes to drug-seeking behaviors. We have employed astrocyte-specific AAV5-GfaABC1D-Rpl22-HA (Addgene #111811) to

immunoprecipitate mRNAs from NAc astrocytes following long-access cocaine vs. saline self-administration, at withdrawal days 1 and 45 for RNA-Seq analyses. Results indicate significant differences in NAc astrocyte gene expression following cocaine self-administration at abstinence day 1. The majority of differentially expressed genes showed decreased expression, with a few genes significantly upregulated in cocaine-administering rats. Gene ontology analyses showed that the identified differentially expressed genes were primarily involved in cellular processes including transcriptional regulation and GTPase activity, among others. Extended comparative analysis of long abstinence is ongoing. Near term studies will also analyze expression changes in female rats, as our lab has demonstrated sex differences in cocaine induced NAc astrocyte structural changes (Kim et al., eNeuro 2022). Ultimately, these studies will provide insight to how cocaine affects astrocytes, both structurally and functionally, and how NAc astrocyte dysfunction increases susceptibility to augmented drug-seeking behaviors across abstinence.

Disclosures: J.P. Franklin: None. **K.J. Reissner:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.11/C37

Topic: B.09. Glial Mechanisms

Support: NIDA 5P01DA047233
T32DA053558-02

Title: Astrocytic CREB Regulates Transcriptomic and Behavioral Responses to Cocaine

Authors: *L. M. HOLT[1], A. M. MINIER-TORIBIO[2], R. FUTAMARA[2], C. J. BROWNE[2], F. J. MARTINEZ-RIVERA[2], T. MARKOVIC[2], T. M. GYLES[2], E. M. PARISE[2], S.-Y. YEH[2], M. ESTILL[2], M. RIVERA[2], C. AZIZIAN[2], E. J. NESTLER[3];
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Abstract: Drug addiction represents an enormous healthcare burden. To better understand its biological underpinnings, investigations of the transcriptional response to drugs of abuse have demonstrated lasting changes in gene expression throughout the brain's reward circuitry. Historically focused on neurons, emerging evidence increasingly indicates that astrocytes are also involved in disorders of the nervous system, including addiction. However, the astrocyte-specific transcriptome and its regulation following exposure to drugs of abuse have not yet been investigated. We utilized whole cell sorting of astrocytes and RNA-sequencing to characterize the astrocyte transcriptome in several key brain regions involved in reward-processing, including the nucleus accumbens and prefrontal cortex, following cocaine self-administration, withdrawal, and "relapse" in mice. We determined that astrocytes exhibit a robust transcriptional response,

including regionally- and contextually-specific transcriptional signatures. Interestingly, bioinformatic analysis revealed CREB as a highly-ranked predicted upstream regulator, and CUT&RUN-sequencing identified increased association of CREB bound at DNA in astrocytes following cocaine administration. Viral-mediated manipulation of CREB activity selectively in NAc astrocytes, in combination with a variety of addiction-related behaviors including conditioned place preference and self-administration, reveals that astrocytic CREB increases the rewarding and reinforcing properties of cocaine. Interestingly, this effect is sex-specific, with no change in preference found in females. Together, these data demonstrate that the astrocyte transcriptome responds robustly to cocaine administration and indicates, for the first time, that CREB is a cocaine-induced transcriptional regulator in astrocytes that increases the rewarding properties of cocaine. These findings are particularly interesting, as previously published work demonstrates opposite effects with neuronal CREB in NAc: increased neuronal CREB activity results in cocaine aversion. Ongoing studies are investigating the molecular mechanism by which astrocytic CREB regulates addiction-related behaviors.

Disclosures: **L.M. Holt:** None. **A.M. Minier-Toribio:** None. **R. Futamara:** None. **C.J. Browne:** None. **F.J. Martinez-Rivera:** None. **T. Markovic:** None. **T.M. Gyles:** None. **E.M. Parise:** None. **S. Yeh:** None. **M. Estill:** None. **M. Rivera:** None. **C. Azizian:** None. **E.J. Nestler:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.12/C38

Topic: B.09. Glial Mechanisms

Support: NIH Grant R21 DA052447

Title: Reducing Astrocyte-calcium Signaling in the Nucleus Accumbens Increases Cocaine Self-administration Behavior

Authors: *G. A. LARAIA, J. W. VANRYZIN, K. J. REISSNER;
Psychology and Neurosci., Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Accumulating evidence suggests that astrocytes are critical for reward processing and are implicated in substance use disorders in the brain. Rat cocaine self-administration is associated with long-lasting changes in astrocyte structure and activity, particularly within the nucleus accumbens (NAc). Moreover, pharmacological manipulation of astrocytes can reduce cocaine seeking behaviors. A critical component of astrocyte function is signal transduction via Ca2+ signaling. In order to investigate the role of nucleus accumbens astrocyte Ca2+ signaling in cocaine self-administration and seeking, we employed AAV5 hPMCA2 (CalEx) under control of the astrocyte-specific GfaABC1D promoter, to deplete NAc astrocyte Ca2+. AAV5 GfaABC1D-Lck-mCherry was employed as negative control. Following jugular catheterization and viral

infusion, rats were trained in either short-access (ShA, 2h/day) or long-access (LgA, 6h/day) cocaine self-administration, followed by home cage abstinence. No effect of hPMCA2 was observed during ShA self-administration; however, hPMCA2 expression resulted in a significance increase in cocaine self-administration during LgA access. Following 45 days of abstinence, no difference was observed between hPMCA2 and Lck-mCherry rats in cocaine seeking behavior. Specificity of expression was confirmed using immunohistochemistry. These results collectively indicate that depletion of NAc astrocyte Ca2+ results in modified reward processing under conditions of extended access. Future studies using behavioral economics may more fully detail the nature of the modified reward processing, and the role of astrocyte Ca2+ signaling in substance use disorders.

Disclosures: G.A. Laraia: None. **J.W. VanRyzin:** None. **K.J. Reissner:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.13/C39

Topic: B.09. Glial Mechanisms

Support: R21 DA055781

Title: Role of GSCAN Identified Genes in the Astrocytic Response to Nicotine

Authors: *A. LOMBARDI[1,2], M. BOWER[2], C. BORSKI[2,3], K. KASTENGREN[2,3], M. EHRINGER[2,3], J. STITZEL[2,3], C. HOEFFER[2,3];
[2]Integrative Physiol., [3]Inst. for Behavioral Genet., [1]Univ. of Colorado Boulder, Boulder, CO

Abstract: Improved understanding of nicotine neurobiology is needed to reduce or prevent chronic addiction, the detrimental effects of nicotine withdrawal, and increase successful cessation of use. Nicotine use Genome wide association studies (GWAS) suggest an astrocytic role for nicotine responses. Previously, we found that *Akt2* expression is restricted to astrocytes in mice and humans and may play a role in the nicotinic responses of astrocytes. The current study aims to identify additional astrocyte-expressed genes that alter nicotine's effect on astrocytes and contribute to nicotine use behaviors. To identify genes of interest (GOI)s, we selected genes from TWAS results from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) significantly associated with cigarettes per day (CPD) and smoking cessation (CS) that were also expressed in human and mouse astrocytes. The genes that met these criteria were further prioritized by whether they also were associated with CPD and SC in additional analyses including Pascal, DEPICT, and fine mapping. Using a CRISPRi approach to knockdown GOI expression, we are screening 25-50 of these smoking-related, astrocyte-expressed genes. Using area analysis, we are assessing the role of the GOI on astrocyte size and morphology in primary mouse astrocyte cultures following nicotine treatment. The screen will identify GOIs for generating new mouse models to assess the role of the astrocyte-expressed

gene on nicotine behaviors and *in vivo* astrocyte response to nicotine. We have already found a promising gene target, *Clusterin*, that when knocked down blunts the astrocytic response to nicotine. These results will allow for the identification of potential novel drug targets and will improve the current understanding of the astrocytic response to nicotine.

Disclosures: A. Lombardi: None. **M. Bower:** None. **C. Borski:** None. **K. Kastengren:** None. **M. Ehringer:** None. **J. Stitzel:** None. **C. Hoeffer:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.14/C40

Topic: B.09. Glial Mechanisms

Support: R01AA016959
F31AA030720-01

Title: Measures of Astrocyte Morphology Subtly Altered in a Rat Model of Alcohol Use Disorder

Authors: *S. P. GUERIN, K. NIXON;
Univ. of Texas at Austin, Austin, TX

Abstract: Excessive alcohol consumption consistent with an alcohol use disorder (AUD) can lead to cognitive impairments that may be caused by structural changes in the brain. These changes can include reactivity in glial cells such as astrocytes. This study investigates morphological changes in astrocytes of male and female rats exposed to ethanol using GFAP to label branches and S100B to label the soma. Adult rats (n=8 per group, PND 65-70; ~240g females, ~350g males) were subjected to 4 days of binge-like alcohol exposure. Rats received ethanol (25% w/v in Vanilla Ensure Plus) or isocaloric control diet 3 times/day for 4 days. Doses of ethanol were adjusted based on a behavior intoxication (9.2 ± 1.4 g/kg/day for males; 9.5 ± 1.2 g/kg/day for females) resulting in blood ethanol concentrations that were similar for both sexes (338.8 ± 70.2 mg/dl for males; 354.3 ± 29.7 mg/dl for females). Withdrawal behaviors were observed from 10-27 hours (30 min on/off) after the last dose of ethanol. Following a week of abstinence from ethanol, animals were transcardially perfused, brains were removed and postfixed in PFA, and sectioned in 12 series at 40µm. A laser scanning confocal microscope was used to take 60x z-stacks of the hilus of the hippocampus, the entorhinal cortex, and the basolateral amygdala. Imaris software was used to reconstruct all GFAP labeled filaments from S100B labeled starting points, which allows for better discrimination of individual astrocytes compared to methods that use GFAP only. Measures of astrocyte morphology were examined, including the area of each astrocyte and the sum of branch lengths. When examining the sum of filament branch lengths in astrocytes, there was a main effect for ethanol treatment in the entorhinal cortex ($p<0.001$) and an interaction effect between sex and treatment ($p<.05$), with

ethanol-exposed female rats having a significant increase in length compared to controls ($p<0.001$). Astrocyte area was also significantly altered by ethanol treatment in the entorhinal cortex ($p<0.05$), but only ethanol-exposed males had a significant increase in area compared to controls ($p<0.05$). There were no significant morphological differences in the amygdala or hippocampus, and astrocyte number was not altered in any of the brain regions. Changes to morphology in the parameters examined were subtle: although morphological parameters were increased in nearly all brain regions, most of these changes were not statistically significant. These results suggest that the phenotype of alcohol-induced reactive astrocytes is unique compared to other pathologies where more robust changes to GFAP are observed.

Disclosures: S.P. Guerin: None. **K. Nixon:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.15/C41

Topic: B.09. Glial Mechanisms

Support: CRCHUM - Bourse de Formation
Université de Montreal - Leadership Bourse
FRQS

Title: The effect of Early-Life Stress on lateral hypothalamic astrocytes and sleep-wake behaviours.

Authors: *L. DEPAAUW-HOLT, S. HAMANE, A. BOSSON, B. ROGERS, C. MURPHY-ROYAL;
Neurosci., Ctr. hospitalier de l'Université de Montréal, Montreal, QC, Canada

Abstract: Astrocytes regulate several important processes in the brain to maintain synaptic transmission and behaviour. The metabolic support role of astrocytes has been shown to coordinate many complex behaviours including sleep-wake cycles. Specifically, astrocytes in the lateral hypothalamus modulate the excitability of orexin neurons by dynamically controlling the availability of energy substrates across night and day to drive sleep-wake cycles. Furthermore, local energetic substrate shuttling to neurons is significantly impaired in conditions of stress, in a glucocorticoid dependant manner. Considering the overwhelming prevalence of sleep-wake perturbations in stress related psychiatric disorders, **we hypothesise that stress, specifically elevations in blood glucocorticoids, impacts lateral hypothalamic astrocytes to influence sleep-wake behaviours.** To determine the impact of stress we employed an early life stress (ELS) paradigm, which significantly increases blood glucocorticoids in adulthood. We then examined the effects of ELS induced elevations in blood corticosterone on astrocyte morphology in the lateral hypothalamus. ELS increased nuclear translocation of astrocyte glucocorticoid receptors, suggestive of increased receptor activity in these cells, that was associated with

reduced expression of astrocytic proteins linked to metabolic support function. Next, we examined the impact of ELS on lateral hypothalamic-dependent behaviours and determine the role of astrocyte-specific glucocorticoid signalling in mediating stress-induced sleep-wake disturbances. To directly implicate astrocyte glucocorticoid receptors in ELS induced behavioural dysfunction we carried out stereotaxic surgeries injecting AAV2/5-GfaABC1D-Cre into the lateral hypothalamus of glucocorticoid receptor (*Nr3c1*)-floxed mice. Following astrocyte-specific GR-Knock Out (KO), we observed a significant alteration in lateral hypothalamus-dependent behaviours in a sex-specific manner, without any alterations in anxiety-like behaviours or basal metabolic function. In sum, these data identify a unique role for astrocyte glucocorticoid receptors in stress-induced sleep-wake behavioural impairment. Our preliminary observations suggest that ELS perturbs astrocyte metabolic network function which in turn can influence the supply of energy substrates to orexin neurons and underlies stress-induced behavioural dysfunction.

Disclosures: L. Depaauw-Holt: None. **S. Hamane:** None. **A. Bosson:** None. **B. Rogers:** None. **C. Murphy-Royal:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.16/C42

Topic: B.09. Glial Mechanisms

Support: Sentinel North Research ChairSentinel North Research Chair to Caroline Menard to Caroline Menard
NeuroQuebec PhD scholarships
CIHR Grant 427011

Title: Early-life adversity induces blood-brain barrier alterations contributing to stress responses in adulthood

Authors: *J. L. SOLANO LÓPEZ[1,2], B. DAIGLE[1,2], M.-È. BOSSÉ[1,2], V. LÉVESQUE[1,2], A. CADORET[1,2], L. BANDEIRA BINDER[1,2], M. LEBEL[2], C. MENARD[1,2];
[1]Univ. Laval, Quebec, QC, Canada; [2]CERVO, Brain Res. Ctr., Quebec, QC, Canada

Abstract: Early-life adversity (ELA) events, like physical and emotional abuse or parental neglect, can occur during critical developmental stages, altering the vulnerability threshold to stressful events. Indeed, ELA can calibrate an individual's future response to stress, by either improving or impairing coping abilities and in some cases, lead to the development of major depressive disorder (MDD) in adulthood. Neurovascular adaptations modulate cognition, stress responses, and mood. Loss of blood-brain barrier (BBB) integrity, which is formed by endothelial cells, astrocyte endfeet ensheathing the vessels, pericytes, and a basement membrane, has been implicated in affective disorders, such as depression, which can arise from chronic

stress. Alterations in astrocyte endfeet have been described in rodents after chronic stress exposure and in MDD postmortem brain samples. During childhood, the BBB goes through critical maturation stages, but it remains unknown if ELA could impact the brain vasculature making it vulnerable to subsequent challenges. The long-term effects of ELA and its interaction with chronic social defeat stress (CSDS) were thus evaluated. Male and female mice were exposed at post-natal day 10, to a 10-day ELA period of maternal separation and limited bedding/nesting. At the end of the ELA period, the animals were group-housed with access to a house, toys, bedding, and nesting material. Subsequently, during adulthood, the animals were subjected to 10-day CSDS (week 8). 24h after the last defeat bout, the stress response was tested with a social interaction test, and anxiety with the elevated plus maze. Punches from brain areas regulating reward, mood, and emotions were collected for qPCR analysis. Interestingly, ELA induced anxiety-like behaviors in males but not in females. ELA combined with CSDS did not exacerbate vulnerability to stress, in fact, it increased the proportion of resilient animals in both males and females. BBB transcriptomic profiling revealed sex-specific differences in astrocytic function, endothelial tight junctions, and glucocorticoid signaling. ELA and/or CSDS exposure produced distinct patterns of neurovascular gene expression. These results indicate that ELA can modulate stress responses when facing emotional challenges in adulthood, possibly through long-lasting changes of BBB properties via the glucocorticoid system and astrocyte's function. It also suggests that access to an enriched environment after ELA could dampen its deleterious impact later in life.

Disclosures: **J.L. Solano López:** None. **B. Daigle:** None. **M. Bossé:** None. **V. Lévesque:** None. **A. Cadoret:** None. **L. Bandeira Binder:** None. **M. Lebel:** None. **C. Menard:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.17/C43

Topic: B.09. Glial Mechanisms

Support: CIHR grant 41204

Title: Astrocyte glucocorticoid signalling mediates cognitive impairment induced by early-life-stress

Authors: I. ADEDIPE[1], L. DEPAAUW-HOLT[1], ***M. GUAYASAMIN**[2,1], O. GHENISSA[1], J. LATRAVERSE-ARQUILLA[1], J. VAUGEOIS[1], M. DUQUENNE[1], B. ROGERS[1], S. PEYRARD[1], A. BOSSON[1], C. MURPHY-ROYAL[1];
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Abstract: Both human and rodent studies have provided compelling evidence for the long-lasting effects of adverse early-life experiences, highlighting enhanced susceptibility to subsequent stressors presented later in life. ELS has widespread effects across the brain and can influence many neural circuits including those involved in threat detection, emotion, cognitive processing, and reward seeking behaviors. Research in this domain has predominantly focused upon investigating the effects of stress on neuronal cells and the consequences for behaviour. However, the links between stress, brain circuits and behaviour remain tenuous, and the contribution of distinct brain cells, including astrocytes, remains largely untested. Glial cells, which comprise approximately half the cell population in the brain have been shown to directly regulate synaptic transmission and plasticity, thereby influencing many discrete behaviours. Despite the abundance of research suggesting important roles for astrocytes in regulating affective states, fear, and reward seeking behaviors, whether astrocyte dysfunction prompts stress-induced behavioral impairments remains unknown. To answer this question, we performed behavioural tests targeting the lateral amygdala, a brain region involved with threat detection and associative learning that is acutely sensitive to stress. Using auditory discriminative fear conditioning, an amygdala-dependent behavioural task, we find that ELS impairs discrimination of neutral from aversive auditory cues. This was associated with impaired synaptic plasticity in cortico-amygdala circuits, recorded in acute brain slices. We characterised the impact of ELS on astrocytes in the lateral amygdala revealing changes in specific proteins associated with morphological reorganisation and astrocyte network function. Genetic disruption of astrocyte function, specifically in the lateral amygdala, recapitulated ELS-induced behavioural and synaptic phenotypes, supporting the hypothesis that astrocytes strongly contribute to the impact of stress on neural circuits. Finally, we reveal that attenuating glucocorticoid signalling in lateral amygdala astrocytes fully rescued the impact of ELS on cognition, with a marked improvement in auditory discrimination. Together, these findings identify astrocytes as key elements regulating amygdala-dependent affective memory and highlight astrocytes as central mediators of the long-term impact of stress on amygdala circuit function.

Disclosures: I. Adedipe: None. **L. Depaauw-Holt:** None. **M. Guayasamin:** None. **O. Ghenissa:** None. **J. Latraverse-Arquilla:** None. **J. Vaugeois:** None. **M. Duquenne:** None. **B. Rogers:** None. **S. Peyrard:** None. **A. Bosson:** None. **C. Murphy-Royal:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.18/C44

Topic: B.09. Glial Mechanisms

Support: JP20dm0107099
JP22zf0127001
JP20km0105001
JP20km0105002

20K07962
JPMJSP2114

Title: Stress causes abnormalities in the production and release of beta hydroxybutyrate in hepatic cells and astrocytes

Authors: *S. SATO, Z. YU, H. TOMITA;
Tohoku Univ., Sendai, Japan

Abstract: Beta-hydroxybutyrate (BHB) is a major ketone body synthesized mainly in the liver mitochondria and is associated with stress and severity of depression in humans. It is known to alleviate depressive-like behaviors in mouse models of depression. It has also been shown to be produced not only in the liver but also in astrocytes, but the effect of stress on the production function is unknown. First, we used nuclear magnetic resonance spectroscopy to analyze and measure plasma BHB, ketogenic and glucogenic amino acids selected from the Tohoku Medical Megabank Project Community-Based Cohort Study. The Center for Epidemiologic Studies Depression Scale (CES-D) was utilized to select adult participants with depressive symptoms (CES-D $\geq$ 16; n = 5722) and control participants (CES-D < 16; n = 18,150). We observed significantly reduced plasma BHB (Tukey-Kramer HSD post hoc test: $P < .008$), leucine ($P < .001$), and tryptophan ($P < .008$) levels in participants with depressive symptoms. Second, we used acute and chronic social defeat stress (SDS) in C57BL6/N mice to investigate the effect of stress on BHB production. For the chronic SDS session, the C57BL/6 mice were exposed to a different CD1 aggressor mouse for 10 min every day for 10 consecutive days by removing the clear, perforated plexiglas divider. The acute SDS session was composed of three 10-min exposures to SDS, within a single day, and 5-min intervals between each exposure. BHB levels in serum ($n = 15$, $P < .001$) and mitochondria of prefrontal cortex (PFC) ($n = 10$, $P < .001$), but not in hepatic mitochondria, were significantly increased after acute SDS. After chronic SDS, BHB level in liver mitochondria was significantly reduced (control: $n = 18$, SDS: $n = 35$, $P < .01$), whereas no significant difference in serum and PFC mitochondria. In addition, transcription levels of monocarboxylic acid transporter 1 (Mct1), major molecules relevant to BHB transporter, were significantly decreased in the liver (control: $n = 10$, SDS: $n = 9$, $P < .001$) and PFC (control: $n = 12$, SDS: $n = 20$, $P < .05$) after chronic SDS exposure. Furthermore, we administered corticosterone, a stress hormone, to the human astrocytoma U251-MG cells. Corticosterone induced significantly higher amounts of BHB in the mitochondria ($n = 6$, $P < .05$) and cytoplasm ($n = 6$, $P = .05$) but not in the culture medium. In addition, the transcript level of the BHB transporter Mct2 ($n = 12$, $P < .001$) and Mct4 ($n = 12$, $P < .01$) were significantly decreased by corticosterone treatment. Our findings suggest that stress causes abnormalities in the production and release of BHB in the hepatic cells and astrocytes, potentially associated with the dysfunction of monocarboxylate transporters.

Disclosures: **S. Sato:** None. **Z. Yu:** None. **H. Tomita:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.19/C45

Topic: B.09. Glial Mechanisms

Support: KAUST Research Grant

Title: Effect of Stress and Corticosterone on Astrocyte-Neuron Lactate Shuttle in Depression

Authors: *F. CHAMAA, **X. LIN**, H. FIUMELLI, P. J. MAGISTRETTI;
King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Depression, a psychiatric disorder influenced by stress and high corticosterone levels, has been associated with reduction in brain glucose metabolism (Su et al. BMC Psychiatry 2014). The astrocyte-neuron lactate shuttle (ANLS) plays a crucial role in this context, and its dysfunction has been implicated in the pathophysiology of depression (Carrard et al. Mol Psychiatry, 2021). Our objective is to explore the impact of stress and corticosterone on the impairment of astrocyte-neuron metabolic coupling and the potential for restoration through lactate treatment, both *in vitro* and *in vivo*. The antidepressant effect of lactate has been previously shown in three models of depression in mice, the forced swim test, the open space forced swim test and chronic corticosterone treatment (Carrard et al. Mol Psychiatry 2018 and 2021). In the present study, prolonged exposure of mouse neocortical astrocytic cultures to corticosterone resulted in the upregulation of thioredoxin-interacting protein (TXNIP), a pathological marker associated with dysfunction in glucose and lipid metabolism. Furthermore, corticosterone led to a decrease in glucose uptake in these cells, along with downregulation of glucose transporter-1 (GLUT-1) expression at the cell membrane level, and lactate monocarboxylate transporter-4 (MCT-4) at both the mRNA and protein levels. Moreover, there was a reduction in lactate release from astrocytes, indicating impairment in the ANLS. *In vivo* experiments using mouse models of chronic unpredictable stress (CUS) or corticosterone-induced depression demonstrated increased anxiety and social avoidance, as evidenced by behavioral tests including the social interaction test. Treatment with lactate in both models promoted resilience to stress and anxiety, while also rescuing social avoidance to levels comparable to control mice. Currently, we are examining changes in the expression of genes related to energy metabolism in the hippocampus and prefrontal cortex in the two depression models, with or without lactate treatment. The alterations observed in astrocytes suggest that the ANLS pathway is a crucial target in stress and mood disorders.

Disclosures: **F. Chamaa:** None. **X. Lin:** None. **H. Fiumelli:** None. **P.J. Magistretti:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.20/C46

Topic: B.09. Glial Mechanisms

Title: The Role of Astrocyte Calcium Signaling in Anxiety-like Behavior

Authors: *E. KIM[1], M. MA[2], X. YU[1];
[1]Neurosci. Program, [2]Sch. of Mol. & Cell. Biol., UIUC, Urbana, IL

Abstract: Anxiety disorders are one of the most common psychiatric diseases and are highly comorbid with other mental health diseases, such as major depressive disorder (MDD) and bipolar disorder (BD). Studies showed that patients with anxiety disorders have a detrimental impact on the quality of life across their lifespan. Unfortunately, current anxiolytic medications are ineffective since around half of patients fail to respond to initial treatment. In order to develop novel therapeutic treatments for anxiety disorders, understanding the neurobiological mechanism is crucial. The medial prefrontal cortex (mPFC) enacts an essential role as a central hub of microcircuits that regulate emotions including anxiety. The dysfunction of the mPFC has been reported in both human anxiety disorder patients and animal models. For example, in a rodent anxiety model induced by social defeat stress (SDS), increased glutamatergic neurotransmission was shown in mPFC. Until now, most studies have focused on neuronal changes to apprehend the mechanisms underlying anxiety disorders, while little is known about non-neuronal changes. Neurons are not the only cells in the brain controlling emotions. Astrocytes are one of the most abundant cells in the brain and interact closely with neurons and other glial cells. Dissimilar to neurons, astrocytes utilize intracellular calcium signals rather than electrical signals to interact with other cells. Previous studies have shown that altered astrocyte calcium signaling in the striatum caused synaptic and circuit-level changes, ultimately leading to abnormal repetitive behavior. However, the role of astrocytes in mPFC and their effects on anxiety-like behavior are largely unknown. To address this question, a newly developed transgenic mouse line $CalEx^{flox}$ that can extrude intracellular calcium signals in astrocytes was executed to validate astrocyte function in the mPFC and anxiety-like behavior. We believe that comprehending the contribution of astrocyte calcium signaling in anxiety-like behavior would be conducive to providing potential therapeutic targets for anxiety disorders.

Disclosures: E. Kim: None. **M. Ma:** None. **X. Yu:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.21/C47

Topic: B.09. Glial Mechanisms

Title: Inactivation of Astrocytes in Dentate Gyrus Results in Anxiolytic-like and Cognitive Phenotypes

Authors: *M. WANG[1,4], M. KAMBALI[2], R. NAGARAJAN[2], J. LYU[1,4], X. YU[3], U. RUDOLPH[2];

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Abstract: Astrocytes are increasingly being recognized as having important roles in regulating the functional output of neuronal circuits, e.g., by sensing and modifying synaptic activity. In the hippocampus, astrocytes have been found to modulate long-term potentiation in CA1 and dentate gyrus (DG), and it has been reported that in a mouse model of Alzheimer's disease loss of tau homeostasis in dentate gyrus hilar astrocytes results in spatial memory deficits. Our previous studies have shown that additional copies of the *Gldc* gene encoding the glycine-degrading enzyme glycine decarboxylase, which in the brain is expressed only in astrocytes, resulted in a deficit in long-term potentiation in the dentate gyrus and schizophrenia-like phenotypes. These findings raise the question whether functions of the DG relating to learning and memory and to anxiety-related behaviors may be modulated by astrocytes. To evaluate the functional significance of the activity of astrocytes in dentate gyrus, we expressed the calcium extrusion pump hPMCA2w/b (CalEx) in dentate gyrus astrocytes. CalEx removes calcium from the astrocytes and thus disrupts any calcium-dependent astrocytic function. A viral construct expressing CalEx or tdTomato (for control group) with the astrocyte-specific *Gfa*ABC$_1$D promoter was stereotaxically injected into the DG hilus of 3 months-old male and female C57BL/6J mice. After a recovery period of 3 weeks behavioral experiments were performed, including elevated plus maze, open field test, light/dark box, Y-maze, social interaction test, Morris water maze, as well as latent inhibition and Pre-pulse inhibition / startle habituation tests. In the elevated plus maze test, female mice injected with CalEx-expressing virus showed less anxiety-like behaviors compared to mice injected with the control virus. CalEx-expressing mice also displayed enhanced performance in reversal learning phase of the Morris water maze and a latent inhibition deficit. We propose that astrocytes in dentate gyrus may modulate anxiety-like behavior in mice, and that normal astrocytic function is essential for some aspects of memory tasks facilitated by the dentate gyrus and possibly play a critical role in memory tasks that involve memory interference.

Disclosures: M. Wang: None. **M. Kambali:** None. **R. Nagarajan:** None. **J. Lyu:** None. **X. Yu:** None. **U. Rudolph:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.22/C48

Topic: B.09. Glial Mechanisms

Title: Investigating the morphology and activation of microglia and astrocytes via chronic stress-induced inflammation in the hippocampus

Authors: *A. Y. ZHANG, E. ELIAS, M. T. MANNERS;
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Abstract: Investigating morphology and activation of microglia and astrocyte via chronic stress-induced inflammation in the hippocampus
Authors**A.Y. Zhang**, E. Elias, M.T. Manners; College of Science and Mathematics, Rowan University, Glassboro, NJ
Disclosures**A.Y. Zhang**: None; **E. Elias**: None; **M.T. Manners**: None.
Abstract Chronic stress is a major precursor to various neurodegenerative disorders. Emerging evidence suggests that chronic stress is associated with increased inflammation in the brain. However, the bidirectional association between inflammation and chronic stress has yet to be fully understood. Microglia and astrocytes are key inflammatory regulators in the brain. When activated by inflammation, microglia and astrocytes become neurotoxic and proinflammatory. In this study, we aimed to evaluate the chronic stress-induced inflammation in the hippocampus by examining the morphological and molecular changes of microglia and astrocytes. We conducted the Unpredictable Chronic Mild Stress (UCMS) paradigm to model chronic stress, and lipopolysaccharide (LPS) administration to induce systemic inflammation in mice. Sholl analysis was performed to analyze microglia and astrocytes morphology. Chronic stress induced morphological changes in astrocytes similar to systemic inflammation in the hippocampus. Hippocampal astrocytes were highly ramified with increased branches and branching points from the cell body compared to the control group. However, unlike astrocytes, chronic stress did not induce morphological changes in hippocampal microglia. The finding of this study suggests that chronic stress induces inflammation in the hippocampus through astrocyte activation.

Disclosures: A.Y. Zhang: None. **E. Elias:** None. **M.T. Manners:** None.

Poster

PSTR252. Astrocytes: Mechanisms Underlying Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.23/C49

Topic: B.09. Glial Mechanisms

Support: Brain and Behavior research foundation
CAMH discovery fund
CIHR Grant PGT165852
Campbell Family Mental Health Research Institute

Title: Prefrontal Cortex Astroglia Modulate Anhedonia-like Behavior

Authors: *S. A. CODELUPPI[1], M. XU[2], Y. BANSAL[1], A. E. LEPACK[2], V. DURIC[3], M. CHOW[1], J. MUIR[4], R. C. BAGOT[4], P. LICZNERSKI[2], S. L. WILBER[2], G. SANACORA[2], E. SIBILLE[1], R. S. DUMAN[2], C. J. PITTENGER[2], M. BANASR[1];
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Abstract: Astroglia loss and decreased expression of specific markers expressed by GFAP (glial fibrillary acidic protein)-astroglia have been found in key brain regions such as the prefrontal cortex (PFC) in MDD patients and rodent chronic stress models. In this study, we examined the consequences of PFC GFAP-astroglia ablation on depressive-like behaviours and potential reversal of chronic stress-induced deficits by enhancing PFC GFAP-astroglia activity. GFAP-cre mice infused in the PFC with an AAV5-DOI-CMV-DTR (diphtheria toxin (DT) receptor) were behaviourally assessed following i.p. injection with DT in several tests measuring anhedonia- and anxiety-like behaviors. We found that PFC astroglial ablation induced significant anhedonia- but not anxiety-like deficits. We also infused wild-type mice with an AAV5-GFAP-DREADD (designer receptor exclusively activated by designer drug) Gq in the PFC to activate GFAP-astrocytes upon clozapine-N-oxide administration. While PFC GFAP activation had no effects at baseline (no stress condition), it reversed the anhedonia-like deficits induced by chronic stress exposure. No reversal of anxiety deficits was observed. After validating increased astroglia activity using Ca^{2+} fiberphotometry following GFAP+ cell activation with CNO we used the same technique to assess in parallel changes in neuronal and astroglial in animals subjected to acute and chronic stress. Our results demonstrate that cortical GFAP-astroglia loss is sufficient to induce anhedonia, that chronic stress-induced anhedonia-like deficits can be reversed by increased GFAP-astroglia activity and that astroglial and neuronal activity are effect by chronic stress. Altogether, our work suggests a critical role of astroglia in the expression and the treatment of key symptoms of MDD.

Disclosures: S.A. Codeluppi: None. **M. Xu:** None. **Y. Bansal:** None. **A.E. Lepack:** A. Employment/Salary (full or part-time):; Bluerock Pharmaceuticals. **V. Duric:** None. **M. Chow:** None. **J. Muir:** None. **R.C. Bagot:** None. **P. Licznerski:** None. **S.L. Wilber:** None. **G. Sanacora:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Johnson & Johnson/Janssen, Merck, Usona Institute. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biohaven Pharmaceuticals, Freedom Biosciences, Gilead, Relmada, Tetricus. F. Consulting Fees (e.g., advisory boards); Ancora, Aptinyx, Atai, Axsome Therapeutics, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Clexio, Cowen, Denovo Biopharma, ECR1, EMA Wellness, Engrail Therapeutics, Freedom Biosciences, Gilgamesh, Intra-Cellular Therapies, Janssen, KOA Health, Levo therapeutics, Lundbeck, Merck, MiCure, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Otsuka, Perception Neuroscience, Praxis Therapeutics, Relmada Therapeutics, Sage Pharmaceuticals, Seelos Pharmaceuticals, Taisho Pharmaceuticals, Valeant, Vistagen Therapeutics, XW Labs. **E. Sibille:** None. **R.S. Duman:** None. **C.J. Pittenger:** 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.; Biohaven, Transcend, Freedom. F. Consulting Fees (e.g., advisory boards); Biohaven Pharmaceuticals, Transcend Therapeutics, Ceruvia Lifesciences, Freedom Biosciences, Nobilis Therapeutics, F-Prime Ventures. **M. Banasr:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.01/C50

Topic: B.09. Glial Mechanisms

Support: NIH Grant RF1AG082314

Title: Microglial Regulation of Motor Cortical Excitability in TDP-43 related neurodegeneration

Authors: *M. XIE, A. UMPIERRE, Y. LIANG, K. HARUWAKA, S. ZHAO, L. WANG, J. ZHENG, D. BOSCO, P. PALLEGAR, A. NGUYEN, L.-J. WU;
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Abstract: Motor cortical hyperexcitability, a well-documented phenomenon observed in the presymptomatic stage of TDP-43 related neurodegeneration, including amyotrophic lateral sclerosis (ALS). However, the underlying mechanisms responsible for sensing and regulating this early motor cortical dysfunction remain unclear. Microglia, the principal resident immune cells in the central nervous system, have recently gained attention for their role in monitoring and modulating neuronal activity under both physiological and pathological conditions. In this study, we investigated the potential involvement of microglia in sensing and regulating neuronal activity and shaping the function of motor cortical circuits in TDP-43 neurodegeneration by using a novel mouse model (rNLS8). We performed longitudinal calcium imaging in awake mice using *in vivo* two-photon microscopy combined with silicon probes to record neuronal activity in the motor cortex and found a dynamic change in neuronal activity during disease progression. Specifically, we observed neuronal hyperactivity at initial stage. Intriguingly, upon microglia ablation, we observed a dramatic calcium overload in motor cortical neurons, leading to a decrease in survival. To elucidate the underlying mechanisms, we examined microglia activation during disease progression and observed significant activation accompanied by distinct morphologies, suggesting functional heterogeneity of microglia in ALS. Furthermore, we performed spatial RNA sequencing to decode the transcriptional profile of the activated microglia. Additionally, we observed direct interactions between microglia and the apical dendrites of motor neurons, implying a complex interplay between microglia and neurons. Together, our results reveal that microglia may mediate neuroprotection by dampening motor cortical excitability in the hTDP-43 overexpression model of ALS-like motor neuron degeneration. This comprehensive investigation may contribute to the early diagnosis of ALS, while also uncovering novel targets for preventing motor neuron degeneration and impeding disease progression.

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Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.02/C51

Topic: B.09. Glial Mechanisms

Support: NIH Grant 7R01AA023797-07

Title: Interaction of Ethanol and polygenetic background in Alcohol Use Disorder in human iPSC derived microglial cell model

Authors: *X. LI[1], A. J. BORELAND[1], A. STILLITANO[1], Y. ABBO[1], R. P. HART[2], Z. P. PANG[1];
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Abstract: Interaction of Ethanol and polygenetic background in Alcohol Use Disorder in human iPSC derived microglial cell model
Xindi Li[1], Andrew J Boreland[1], Alessandro Stillitano[1], Yara Abbo[1], Ronald P. Hart[2], Zhiping P. Pang[1]
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Alcohol exerts diverse effects on the human brain, including alterations in neurotransmitter release and neuroinflammation, which contribute to the development and progression of alcohol use disorders (AUD) in humans. Numerous gene variants linked to AUD have been identified using genome-wide association studies (GWAS). Leveraging insights derived from these GWAS, integrating these variants by creating polygenic risk scores (PRS) has the potential prediction of outcomes associated with AUD. However, the cellular and molecular mechanisms underlying the interaction between ethanol and PRS on AUD in human remains enigmatic.Microglia, resident immune cells within the central nervous system, play a critical role in AUD by regulating neuroinflammatory responses. Here, we utilized induced pluripotent stem cell (iPSC)-derived microglia obtained from individuals with high PRS (HiPRS) and low PRS (LoPRS) of AUD and investigated the impacts of ethanol. Human microglia were generated from yolk sac embryoid bodies derived from 12 iPSC lines (6 HiPRS and 6 LoPRS, both males and females). The application of 20 mM and 75 mM for 7 days led to a significant increase in microglia expressing the active marker $CD68^{+}$, with no notable distinction observed between the HiPRS and LoPRS lines. Interestingly, the HiPRS-microglial cells displayed enhanced phagocytic activity following EtOH exposure, while the LoPRS-microglial cells exhibited reduced phagocytic capacity. Using RNAseq, we identified abundant differentially expressed genes (DEGs) that have the potential to explain the differences in low vs. high AUD PRS human microglial cells. Notably, these DEGs were predominantly enriched in processes associated with extracellular matrix organization, integrin-mediated signaling pathways, and regulation of calcium ion transport. In conclusion, our findings suggest that genetic backgrounds play important roles in determining their response to EtOH exposure. This research provides novel insights into the intricate connection between genetic factors and microglial function in AUD.

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Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.03/C52

Topic: B.09. Glial Mechanisms

Support: NIH/Arkansas INBRE P20 GM103429

Title: Nmes1 is a regulator of neuro-inflammation in cultured murine microglial cells

Authors: *J. SINZI[1], B. BISHOP[3], S. EWING[2], D. DONLEY[2];
[1]Biol. department, [2]Biol., Harding Univ., Searcy, AR; [3]Biol., Harding, Searcy, AR

Abstract: Beta-amyloid42(Aβ42) is a peptide that accumulates in the brain of Alzheimer's disease (AD) patients and is closely associated with disease-potentiating pro-inflammatory responses of microglial cells. While the inflammatory response to Aβ42 is extensively studied, the precise mechanisms and cell signaling pathways that trigger and regulate this response remain poorly understood. Consistent with prior literature, our preliminary data identified Normal mucosa of esophagus-specific1(NMES1) as a putative regulator of microglial activation in response to Aβ42. NMES1 is a mitochondrial cytochrome c oxidase subunit that is increased in cultured microglia by Aβ42. Consistent with its anti-inflammatory properties, NMES1, replaces the NDUFA4 subunit of cytochrome c oxidase, resulting in lower efficiency of electron transport. Paradoxically, decreased mitochondrial respiration is often associated with elevated inflammation, but increased NMES1 is implicated in suppression of inflammation. Therefore, we modulated NAMES1 expression in cultured microglial cells with and without Aβ42 stimulation. Herein we report on the impact of NMES1 of inflammatory markers and metabolic regulation in microglia. Notably, we found that knockdown of NMES1 by silencing RNA, resulted in an increase of the expression of CD68, a marker of inflammatory activation. Together our data is consistent with NMES1 acting as an inflammatory braking mechanism. Overall, we postulate that NMES1 has been previously underappreciated as an inflammatory regulator in microglial cells. However, more work is required to investigate the impact of NMES1 on microglial activation and proinflammatory responses during disease.

Disclosures: **J. sinzi:** None. **B. Bishop:** None. **S. Ewing:** None. **D. Donley:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR253.04/C53

Topic: B.09. Glial Mechanisms

Support: Arkansas INBRE P20 GM103429

Title: Iron suppresses the microRNA, mir-147b in cultured microglia cells, potentiating pro-inflammatory activation to beta-amyloid in vitro

Authors: *B. BISHOP[1], S. EWING[2], E. MORGAN[3], M. VARGUS[3], D. DONLEY[3];
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Abstract: Iron dysregulation in microglia cells promotes dystrophy and modulates activation in response to disease stimuli such as beta-amyloid. Accumulation of beta-amyloid results in chronic microglia activation linked with the progression of Alzheimer's disease (AD). In addition, the buildup of iron is associated with AD progression, and preliminary data finds that iron potentiates microglial activation in response to beta-amyloid. The mechanism(s) of how elevated iron and beta-amyloid converge to induce microglia dysfunction is unclear. To study this intersection, microglia were cultured in iron for three days, then treated with/without beta-amyloid. We completed a proteomic analysis to identify potential intersection points of beta-amyloid and iron. Normal mucosa of esophagus-specific gene 1 (NMES1) was solely identified as being altered between cells stimulated with iron, beta-amyloid, and iron/beta-amyloid. The host gene for the NMES1 protein is *C15orf48,* and it also produces the microRNA mir-147b. NMES1 is a subunit of mitochondrial cytochrome c oxidase and an inflammatory regulator. Our data suggest that iron attenuates the ability of *C15orf48*/NMES1 to regulate microglial activation. Based on the literature and preliminary data, we hypothesize that mir-147b may be a critical mediator of inflammation that is affected by iron. To study this, we transfected cultured microglia with a mir-147b inhibitor. We found that inhibition of this microRNA potentiates the functional response of microglia to beta-amyloid, suggesting its role as an inflammatory regulator. Herein, we specifically report on the impact of mir-147b on oxidative stress and mitochondrial metabolism - which have both been suggested as potentiators of inflammation in AD. More research is needed to fully elucidate the role of mir-147b on microglial activation and to determine the mechanism by which iron alters mir-147b expression. Our data expands on the current understanding of the mechanisms underlying microglial activation states and suggests that iron dysregulation in microglia may be impairing important inflammatory regulators, such as mir-147b, in the context of beta-amyloid activation.

Disclosures: B. Bishop: None. **S. Ewing:** None. **E. Morgan:** None. **M. Vargus:** None. **D. Donley:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.05/C54

Topic: B.09. Glial Mechanisms

Support: NIH/Arkansas INBRE P20GM103429

Title: Regulation of C15orf48 controls microglial inflammation: a role for methylation?

Authors: *G. BING[1], B. BISHOP[2], D. DONLEY[1];
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Abstract: The *C15orf48* gene encodes the NMES1 protein and the microRNA mir-147b, which both are associated with facilitating inflammatory responses of microglia. Microglial cells act as the resident immune cells of the central nervous system. Chronic neuroinflammation resulting, in part, from microglial activation is a pathological hallmark of neurodegenerative diseases, including Alzheimer's Disease (AD). Despite this, if and how *C15orf48* mediates microglial activation is not well understood. There is evidence of transcriptional dysregulation in AD, both globally and at the *C15orf48* locus. Upon stimulation of cultured microglial cells with beta-amyloid, we found that *C15orf48* expression increased, but the addition of iron attenuated the response. This preliminary finding identifies *C15orf48* regulation as a potential intersection point of disease-associated pathways. In cancer cells, the NMES1 gene has been found to be heavily methylated, suggesting that this may be one mechanism of regulation. However, we also identified dysregulation of putative *C15orf48* transcription factors as a result of inflammatory stimuli. Herein, we report the impact of iron and beta-amyloid on regulation of *C15orf48*. It is known that methylation and transcription factor expression are key regulators of gene expression but more research to examine these factors in the context of *C15orf48* expression. This work will provide insight on the significance of *C15orf48* in directing inflammatory responses of microglia.

Disclosures: G. Bing: None. **B. Bishop:** None. **D. Donley:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.06/C55

Topic: B.09. Glial Mechanisms

Title: Effects of early immune activation on microglial metabolism, cytokine release and synaptic pruning

Authors: *A. CAMPOS SALAZAR[1], S. ATI[2], D. M. NGUYEN[2], J. DZIABIS[2], B. DEVLIN[2], C. J. SMITH[3], E. BORDT[4], S. D. BILBO[2];
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Abstract: Early immune activation impacts brain development leading to behavioral impairment. For instance, lipopolysaccharide (LPS) administration at postnatal day 9 leads to male-specific social behavior deficits and mitochondrial changes in microglia. Our laboratory has described a metabolic shift towards glycolysis in microglia underlying early immune activation with LPS administration at postnatal day 9. This metabolic shift highlights the role of mitochondrial respiration and suggests that microglial functions such as synaptic pruning and cytokine expression can be impacted. My goal is to investigate the effects of early immune activation on microglial functions and mitochondria respiration during development and whether these outcomes are impaired persistently later in life. Male and female postnatal day 9 mice were subcutaneously administered 10 mg/kg LPS. Using the three-chamber sociability test, only LPS-treated male mice showed reduced social investigation times compared to saline. Two microglial functions are analyzed in this study: cytokine release and synaptic pruning. Because we have previously shown that the anterior cingulate cortex (ACC) is a critical node in the social behavior network during development, our experiments are initially performed in the ACC 24 hours after LPS injection. Cytokine profiling for pro-inflammatory and anti-inflammatory cytokines is performed using the MesoScale Discovery platform. Changes in synaptic pruning are investigated in the ACC by quantification of synaptic material inside microglial lysosomal content. Mitochondrial respiration is measured by oxygen consumption rate using the seahorse platform. In isolated microglia from the prefrontal cortex, we expect that LPS administration reduces mitochondrial reliance and increases glycolysis. The correlation between mitochondria respiration status and cytokine profile or synaptic pruning in microglia will crystallize the relationship between microglial metabolism and *in vivo* functions. Finally, to evaluate long-term changes, morphometric parameters such as volume and length of microglial mitochondria from ACC of postnatal day 70 mice are quantified using immunohistochemistry. Our study will strengthen the notion that impairment of mitochondrial respiration driven by early immune activation controls microglial functions such as cytokine release and synaptic pruning *in vivo*.

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Poster

PSTR253. Microglia: Disease Mechanisms

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Program #/Poster #: PSTR253.07/C56

Topic: B.09. Glial Mechanisms

Support: NIEHS T32ES007254

Title: Evaluation of microglial-vascular interactions and glial reactivity through morphometric image analyses in a murine model of intranasal nicotine-derived nitrosamine ketone (NNK) treatment using intravital microscopy

Authors: *L. F. OCHOA[1], P. P. VILLARREAL[2], O. D. SOLOMON[5], F. XIA[3], W. ZHANG[3], G. VARGAS[4];
[1]Neurobio., Univ. Of Texas Med. Branch, Galv Neurosci. Grad. Program, Galveston, TX; [2]Neurobio., [3]Ophthalmology & Visual Sci., [4]Neurosci. Cell Biol. and Anat., Univ. of Texas Med. Br., Galveston, TX; [5]The Univ. of Texas Med. Br., Galveston, TX

Abstract: Cigarette Smoke (CS) significantly impacts global quality of life and mortality rates. Nicotine-derived nitrosamine ketone (NNK), a prominent toxin and nicotine metabolite present in CS and e-cigarettes, has been associated with neuroinflammation and lung cancer due to its ability to form DNA adducts and activate nicotinic receptors. Prior investigations using a humanized flow-based in vitro blood-brain barrier (BBB) model have shown that CS extract exposure triggers pro-inflammatory reactions, disrupts BBB function, and compromises endothelial cell viability. However, the specific effects of NNK on the BBB, vascular dynamics, and in vivo microglial dynamics in relation to the vasculature are currently unclear. In this study, we employed 2-photon microscopy (2P) to examine in vivo cellular responses to intranasally administered NNK. Transgenic mice were treated with NNK for acute (4 days) and chronic (12 weeks) exposures. To quantitatively investigate microglial and cerebrovascular dynamics 2P imaging and NNK treatment were done on *CX$_3$CR-1^{GFP}* mice with IP-delivered Evans Blue (EB). Volumetric scans and time series captured spatial features and dynamic responses. Machine learning (ImageJ plugin), combined with an in-house image processing algorithm that segmented features through a combination of morphological and spectral (filter-based) information was used to isolate individual biological components that included microglia soma, microglial processes, engulfed EB localized within the soma, engulfed EB localized to glial processes, and the vasculature, leading to analysis of reactivity, phagocytic activity, and vascular interactions. NNK groups showed disrupted BBB, increased vessel-associated microglia, heterogeneous microglial morphology (reactive near vessels, homeostatic far from vessels), vasoconstriction, vasodilation, microbursts, increased EB uptake in microglia soma and processes compared to PBS controls. The algorithm was similarly applied in a non-GFP neurodegenerative mouse model (3xTG-AD) treated with NNK. EB labeled vessels and autofluorescence delineated cell-like bodies in the parenchyma consistent with lipofuscin spectral properties. This led to analyses indicating NNK-treated mice exhibited heightened vascular leakage, vasospasms and lipofuscin deposition. In summary, we show that implementing segmentation approaches that leverage morphometry in addition to traditional filter-defined channels provides a powerful way to dissect key image features for assessment of the cerebrovascular microenvironment, revealing responses following exposure to a nicotine-associated carcinogen.

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Poster

PSTR253. Microglia: Disease Mechanisms

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Program #/Poster #: PSTR253.08/C57

Topic: B.09. Glial Mechanisms

Support: NIH-R01DA041455
UNC Pharmacological Sciences T32 Training Program
UNC Behavioral and & Integrative Neuroscience Predoctoral Training in Addiction Science T32 Grant

Title: Microglial morphological and phenotypical changes across abstinence following long-access cocaine self-administration

Authors: *T. BELLINGER[1], A. TESTEN[2], J. W. VANRYZIN[3], K. J. REISSNER[4];
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Abstract: A reactive microglial response to drugs of abuse has been implicated in the development and persistence of substance use disorders. However, the full scope of cocaine-mediated microglia responses to rat cocaine self-administration is understudied. Given this, we sought to determine the timeline of nucleus accumbens microglia morphology across abstinence in adult male rats. We utilized a long-access cocaine self-administration paradigm, in which adult male Sprague Dawley rats self-administered cocaine or saline for six hours per day for ten days. Nucleus accumbens core microglia were then analyzed at abstinence days 1, 30, and 45 (AD1/30/45). Immunohistochemistry was performed to detect microglia marker Iba1 and lysosomal marker CD68, together with astrocytes transduced for AAV5 GfaABC1D Lck-GFP. A Zeiss LSM 800 confocal microscope was used to acquire 63x z-stack images. Bitplane Imaris software was utilized to construct three-dimensional filament reconstruction of individual microglia. A number of morphometric features of microglia were collected, including surface area, volume, soma area, soma volume, soma sphericity, and filament number. In the AD1 cohort, a significant decrease was observed in filament number, area to volume ratio, and filament number of dendrite branch points, with a significant increase in soma sphericity. However, results from AD45 (long abstinence) revealed no significant differences in microglia morphometric measurements between cocaine and saline groups. Colocalization of Iba1 with astrocytic Lck-GFP and CD68 was also performed across abstinence, to determine whether microglia phagocytosis might contribute to previously reported astrocyte hypotrophy. AD1 data illustrate a significant increase in somatic Lck-GFP+ inclusions in microglia of cocaine-administered animals compared to saline animals, but no effect of cocaine on colocalization between Iba1 and CD68, or total Lck-GFP inclusions. AD45 data revealed significantly increased colocalization in cocaine-administering rats of Iba1 with Lck-GFP and Iba1 with CD68, with a significant increase in number and volume of Lck-GFP+ inclusions within microglia, suggesting that microglia phagocytosis is heightened at AD45 in cocaine animals. A small but significant increase in the number of microglia as a function of cocaine were observed at all time points. Structural and colocalization analysis of AD30 is ongoing. Cumulative results from this study demonstrate that microglial morphological responses and evidence of microglial phagocytosis are variable across abstinence.

Disclosures: **T. Bellinger:** None. **A. Testen:** None. **J.W. Vanryzin:** None. **K.J. Reissner:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR253.09/C58

Topic: B.09. Glial Mechanisms

Title: Assessing microglia in the Suprachiasmatic Nucleus, Anterior Hypothalamus and Cortex under control and excitotoxic conditions at different times of day

Authors: *D. ACHARYYA, R. A. PROSSER;
Univ. of Tennessee, Knoxville, Knoxville, TN

Abstract: Various pathological conditions generate excitotoxic conditions resulting in cell death. We have found that the suprachiasmatic nucleus (SCN) is more resistant to excitotoxic damage compared to the anterior hypothalamus (AH) and cortex. We have also found time-of-day differences in excitotoxic susceptibility in all three regions. Given that excitotoxic stimuli induce changes in microglia activity, we are investigating whether differences in microglial responses may contribute to the SCN's excitotoxic resiliency and to the day-night susceptibility differences we have observed. Here we investigated overall microglial numbers and morphology (ramified vs. amoeboid), expression of the pro-inflammatory (CD86) vs. anti-inflammatory microglial cell markers (CD206), and release of cytokines from acute brain slices under control and excitotoxic conditions at different times of day. We hypothesized that distinct microglial activity contribute to regional and time-dependent differences in excitotoxic resiliency.To begin assessing regional differences in microglial number, morphology, and pro- vs. anti-inflammatory state,we prepared acute coronal brain slices containing the SCN/AH or cortex from adult male C57Bl/6 mice. At Zeitgeber time 6 (ZT6, where ZT0 = lights-on; ZT12 = lights-off) the slices were left untreated or exposed to NMDA for 1h. Three hours after the treatment ended, the slices were processed for immunohistochemistry and double-stained for the pan-microglia marker IBA1 and either CD86 or CD206. To investigate differences across 24h, we used the same experimental procedure, except that the slices were treated or left untreated at different times of the day: ZT6, ZT12, ZT16 and ZT23. Lastly, we used the same experimental set-up except that we collected media perfusates from acute slices after control/NMDA treatment at ZT6 to assess cytokine release.Our data show that NMDA shifts SCN microglia to a more amoeboid morphology and increases microglia numbers in the cortex. NMDA also decreases the percentage of CD86-expressing microglia in the SCN and AH compared to cortex. We also see differences in microglial morphology between the SCN and AH under control conditions across the 24 hrs. Our cytokine data are still being collected and analyzed. Thus, there appear to be regional differences in microglial activity that could contribute to variability in excitotoxic responses.

Disclosures: **D. Acharyya:** None. **R.A. Prosser:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.10/C59

Topic: B.09. Glial Mechanisms

Support: Grant-in-Aid for Transformative Research Areas (A) "Glia decoding" (20H05897)
Exploratory Research for Advanced Technology (JPMJER1801)

Title: Enhanced expression of microglial Clec7a in the mesial temporal lobe epilepsy

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Abstract: Medial temporal lobe epilepsy (mTLE) is a chronic neurological disorder characterized by seizures resulting from neuronal hyperexcitation. Approximately one third of individuals with mTLE exhibit resistance to antiepileptic seizure medications (Thurman et al., Epilepsia, 2011; Chen Z et al., JAMA Neurol, 2018). Recently, the involvement of glial cells, such as microglia and astrocytes, in the pathogenesis of mTLE has garnered attention. Glial cells play a pivotal role in maintaining neuronal activity, and it has been postulated that their dysfunction contributes to the development of epileptic seizures. For instance, it has been hypothesized that an exaggerated inflammatory response in microglia might increase neuronal excitability and exacerbate epileptic symptoms (Vezzani et al., Nat Rev Neurol, 2011). However, the precise mechanisms underlying this phenomenon remain elusive, necessitating a comprehensive understanding of the molecular mechanisms by which microglial responses in mTLE contribute to epilepsy pathogenesis (Hiragi et al., Cells, 2018; Andoh et al., Journal of Clinical Medicine, 2019).Here, we performed RNA sequencing on the hippocampus from the mTLE mice to identify microglial genes involved in the pathogenesis of mTLE. We focused on Clec7a, a microglial gene whose expression is upregulated in mTLE. Clec7a is a single transmembrane receptor expressed in myeloid cells. Previous studies have indicated that Clec7a is specifically upregulated in microglia in neurodegenerative diseases such as Alzheimer's disease (Keren-Shaul et al., Cell, 2017). However, the role of microglial Clec7a in central nervous system (CNS) diseases remains unclear (Deerhake et al., Trends Immunol, 2021). Immunohistochemical staining revealed enhanced expression of Clec7a in microglia in the hippocampus two weeks after inducing seizures in the mTLE mouse model. Using single-cell RNA sequencing-based analysis and primary cultures of microglia, we found that the expression of the proinflammatory cytokine TNFα is upregulated downstream of Clec7a. Furthermore, pharmacological investigations employing a glial co-culture system revealed that Clec7a leads to the phosphorylation of ERK in microglia. These findings suggest that in the context of mTLE, microglial Clec7a contributes to microglial survival, proliferation, and inflammatory responses,

potentially influencing neuronal cell death in the hippocampus and the development of epileptic seizures.

Disclosures: **T. Kawana:** None. **Y. Ikegaya:** None. **R. Koyama:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR253.11/C60

Topic: B.09. Glial Mechanisms

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NIH R01 EY026629
UTMB Cecil H. and Ida M. Green Distinguished Chair in Neuroscience endowment
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UTMB Predoctoral Kempner Fellowship
NIEHS T32 Training Grant Support T32ES007254

Title: Intravital microscopy study of microglial vasculature interactions and vascular dysregulation in an experimental cerebral malaria model reveals protective role of microglia.

Authors: *O. SOLOMON[1,2], P. VILLARREAL[3], N. D. DOMINGO[7], L. OCHOA[4], A. E. CARDONA[9], R. STEPHENS[7,8,5,6], G. VARGAS[4,2];
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Abstract: Cerebral malaria (CM) is the most lethal form of malaria due to a *Plasmodium falciparum* infection involving systemic inflammation. Children under the age of five residing in Africa south of the Sahara are most susceptible to developing this condition. It is a condition associated with neurological deficits that are evident even in survivors. Experimental models of CM indicate this condition involves hypercoagulation and microgliosis, studied previously in late disease. The role of microglia in disease pathogenesis, as well as the interplay between coagulation and microgliosis, have not been elucidated. This study sought to investigate the role of microglia in eCM and how the microglial responses relate to hypercoagulation. Intravital multiphoton microscopy (IVM) was performed on IL-10$^{-/-}$CX3CR1$^{GFP/-}$CCR2$^{RFP/-}$ and IL-10$^{-/-}$ murine models infected with *Plasmodium chabaudi* to investigate the interplay between coagulation and microglial-vascular responses. Additionally, a study was performed to deplete microglia using Pexidartinib, a CSF-1R inhibitor incorporated into a custom chow. In comparisons between infected and uninfected animals, IVM coupled with immunohistochemistry

indicated significant reactive microglia near vessels while microglia further away from vessels are less reactive. Studies also indicated in infection an increase in vessel associated microglia and revealed microglia associated with intravascular CCL5+thrombi. Moreover, results showed microglia were actively engulfing fibrinogen and also suggestive of microglial-vascular interaction at play. Findings of microgliosis, coagulation, and associations between microglia and vessels increased in late disease (D7) vs early (D3). Depletion of microglia resulted in increased disease severity denoted by a rapid decline of clinical scores and exacerbated hypothermia beyond that experienced without Pexidartinib. Notably, sagittal brain sections exhibited increased widespread hypercoagulation in the infected microglia-depleted group vs. infected normal chow group (percent area mean: uninfected, normal chow= 8%, infected normal chow= 15%, infected Pexidartinib chow= 25%, P=0.01), suggesting that microglia play an important role in controlling the effects of coagulation to maintain homeostasis.

Disclosures: O. Solomon: None. **P. Villarreal:** None. **N.D. Domingo:** None. **L. Ochoa:** None. **A.E. Cardona:** None. **R. Stephens:** None. **G. Vargas:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.12/C61

Topic: B.09. Glial Mechanisms

Support: NIEHS R00ES033278

Title: Effects of combined gestational exposure to air pollution and maternal stress on microglial interactions with social circuits in male and female offspring

Authors: *M. C. STOEHR[1], J. XUE[1], J. BABALOLA[1], E. T. HICKEY[1], D. M. NGUYEN[2], S. D. BILBO[2], C. J. SMITH[1];
[1]Psychology and Neurosci., Boston Col., Chestnut Hill, MA; [2]Psychology and Neurosci., Duke Univ., Durham, NC

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction, repetitive behaviors, and a sex bias in prevalence (higher in males). Air pollution and maternal stress during pregnancy are both risk factors for ASD. Air pollution disproportionately impacts communities that also experience high levels of psychosocial stress and these exposures may combine to increase overall risk. However, the biological mechanisms by which these exposures increase ASD risk are not fully understood. The social decision-making network (SDMN) is a set of interconnected brain regions critical to the control of social behaviors across many species. Oxytocin (OT) and vasopressin (AVP) are closely related nonapeptides whose receptors are highly expressed within the SDMN and regulate social behavior. Microglia, the resident immune cells of the brain, sculpt neural circuits during development and respond to environmental signals like air pollution. Therefore, we aimed to

investigate whether prenatal exposure to air pollution and maternal stress might alter microglial sculpting of OT and/or AVP in the SDMN. Our lab utilizes a mouse model in which pregnant dams are exposed to combined diesel exhaust particles (DEP) and maternal stress (MS). In the DEP/MS model, we previously found that male offspring show social behavior deficits and shifts in microglial morphology and gene expression. Here, we exposed dams to either DEP/MS or control (CON) and then cross-fostered pups to determine the importance of the postnatal environment. We assessed microglial density and morphology in 3 subregions of the prefrontal cortex and in the lateral septum (LS). We found that in the prelimbic cortex microglial density is lower following DEP/MS as compared to CON ($p = 0.01$). In the LS, microglial density tended to be lower following DEP/MS ($p=0.06$), and density was significantly increased in DEP/MS pups who were cross-fostered to a CON dam on the day of birth ($p=0.04$). Currently, we are investigating whether there are changes in microglial morphology within the PrL and LS. We are also characterizing microglial interactions with OT and AVP systems in critical nodes of the SDMN throughout development and how DEP/MS exposure alters these interactions.

Disclosures: **M.C. Stoehr:** None. **J. Xue:** None. **J. Babalola:** None. **E.T. Hickey:** None. **D.M. Nguyen:** None. **S.D. Bilbo:** None. **C.J. Smith:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.13/C62

Topic: B.09. Glial Mechanisms

Support: NIH Grant AG062716-04

Title: Early life hormone manipulation in rats alters microglial activation in adulthood

Authors: *L. K. DAVIS[1], J. S. DARLING[2], L. K. FONKEN[2];
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Abstract: Microglia play a critical role in the central nervous system during health and disease. Sex differences in microglial activation and morphology have been observed across development, raising valuable questions about the role of sex hormones in microglial function and pathology. Although it is known that hormones are crucial for the appearance of sex differences in microglial function, it is unclear whether sex differences are due to organizational effects of early life hormones or if sex differences in microglia result from the activational wave of hormones during puberty. Understanding the role of hormones on microglial physiology and function may have important implications for treating nervous system disorders. In this study, we examined the role of hormones on microglial activation and morphology across the lifespan. F344 x Brown Norway F1 rats were subcutaneously injected with vehicle or hormone treatments on postnatal day (P) 0 and 1. Females were treated with testosterone to masculinize them; males were treated with the androgen antagonist, Flutamide, to feminize them. Brain tissue was

collected across the lifespan: prepubertal (P30), adulthood (P150), and aged (P700), and microglia were isolated for *ex vivo* assays and immunohistochemistry. Microglia were isolated using a Percoll density gradient and plated with lipopolysaccharide (LPS) before being assessed for proinflammatory cytokine gene expression. We report that early hormone treatment did not affect rat physiology or microglial activation at P30. However, by adulthood, there were changes in physiology and microglial activation such that microglia isolated from vehicle-treated males had elevated pro-inflammatory cytokine gene expression, while flutamide-treated males have reduced inflammatory cytokines. Although female physiology was affected by hormone treatment in adulthood, such that testosterone-treated females were significantly larger than vehicle-treated females, female microglia did not appear affected by hormone treatment. These results suggest that the activational wave of hormones during puberty may be critical for the appearance of sex differences in microglial activation, especially in males. Ongoing work is examining how adult microglial morphology is affected by hormone treatment, as well as assessing how early life hormone treatment alters sex differences in age-related cognitive decline in our aging rats (P700).

Disclosures: **L.K. Davis:** None. **J.S. Darling:** None. **L.K. Fonken:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.14/C63

Topic: B.09. Glial Mechanisms

Support: the Intramural Research Program of the National Institute of Health

Title: Role of synaptic refinement in the pathophysiology of stuttering disorders

Authors: *A. ADECK[1], M. WEINHOLD[3], M. MILLWATER[2], S. SHEIKHBAHAEI[1]; [2]Natl. Inst. of Neurolog. Disorders and Stroke, [1]NIH, Bethesda, MD; [3]Natl. Inst. of Health, Natl. Inst. of Neurolog. Disorders and Strokes, Bethesda, MD

Abstract: Stuttering, a prevalent neurodevelopmental speech disorder, significantly impacts approximately 1% of the adult population in the United States. It manifests as recurrent disruptions in the natural rhythm of speech, characterized by silent blocks, word repetitions, and elongated sounds. Synaptic refinement plays a crucial role in brain development, orchestrating the elimination and preservation of specific synapses in response to fluctuations in neural activity. Disruptions in this process have been associated with neurodevelopmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and Tourette Syndrome. Imaging data in human suggested a deficit in synaptic refinement in individuals who stutter, however, direct experimental evidence has been limited. In this study, we employed viral-vector-assisted circuit mapping, advanced electron and light microscopy, and 3D computer-assisted cellular reconstruction techniques to investigate synaptic pruning in a

mouse model of stuttering (Gnptab-mutant mice). Since reactive microglia cells contribute to synaptic pruning process, we reconstructed microglia cells (immunostained by Iba1 marker) as well as vesicular glutamate transporter 2 (VGLUT2) and vesicular GABA transporter (VGAT) as synaptic proteins in postnatal (P)- 7, 15, and 21. We then examined the localization of VGLUT2 and VGAT with Iba1+ microglia cells. Our preliminary data suggest higher levels of VGAT and VGLUT2 localization within IBA1+ cells in control mice (by 35%, n=10-12 microglia per group per region) compared to *Gnptab-mutant* mice at all ages. The observed pruning deficit may lead to excess synapses. Critical components for neuronal communication, which can significantly impact brain function. Given the integral role of microglia in synaptic pruning during the critical period, our data propose that these glial cells may have a significant involvement in the pathophysiology of stuttering disorder.

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Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.15/D1

Topic: B.09. Glial Mechanisms

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NIH Grant T32DK007245
Michigan Alzheimer's Disease Research Center P30AG072931
NIA Grant 1K99AG071667-01A1

Title: Adipose tissue-derived extracellular vesicles; effects of aging and inflammation in obesity and prediabetes

Authors: *A. ALLOUCH[1,2], S. E. ELZINGA[1,2], R. E. HENN[1,2], E. GLASS[3,4], R. PARENT[3,4], K. GUO[5], F. E. MENDELSON[1,2], J. M. HAYES[1,2], I. WEBBER-DAVIS[1,2], G. G. MURPHY[3,4], J. HUR[5], E. L. FELDMAN[1,2];
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Abstract: Inflammation, particularly adipose tissue inflammation, is commonly associated with multiple diseases and disorders, including obesity, prediabetes, type 2 diabetes, and aging. This inflammation is thought to promote the neurological complications that are common in these disorders. Adipose tissue-derived extracellular vesicles (EVs) are key mediators of cell-cell communication. EVs can cross the blood brain barrier and may promote central nervous system

(CNS) inflammation, potentially via activation of the primary immune cells of the CNS, the microglia. Therefore, our goal was to assess potential inflammatory effects of age and obesity/prediabetes on microglia-adipose crosstalk via EVs. To do this, we induced obesity/prediabetes by feeding young adult (5 weeks of age) or middle aged (1 year of age) male C57BL/6 mice either standard diet (SD) or high fat diet (HFD) for 13 weeks. Metabolic and cognitive phenotyping was performed at terminal and fresh epididymal white adipose tissue from these animals (n=3/group) was used to isolate EVs. HFD-fed animals developed cognitive impairment, which was aggravated by age. We also showed adipose tissue hypertrophy in HFD animals, which was similar in both age groups. Cognitive deficits were accompanied by changes in CNS inflammatory profiles, which varied dependent upon age. Complimentary *in vitro* work in a human microglial cell line (SV40; applied biological materials, British Columbia, Canada) was used to characterize adipose-microglial crosstalk by treating microglia for 24 hours with adipose tissue-derived EVs. Western blots of microglial NFκB protein expression showed increased expression in cells treated with adipose tissue-derived EVs from adult HFD mice, as well as EVs from aged SD fed animals relative to adult SD controls. These data indicate that HFD and age promote cognitive impairment and inflammatory changes. HFD and age may also disrupt adipose-microglia crosstalk via EVs, contributing to an inflammatory environment in the CNS.

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Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.16/Web Only

Topic: B.09. Glial Mechanisms

Support: NIAAA

Title: Microglial priming in orbital frontal cortex of alcohol use disorder

Authors: *L. QIN, R. P. VETRENO, L. G. COLEMAN, Jr, F. T. CREWS;
Univ. North Carolina, Sch. Med., Chapel Hill, NC

Abstract: Microglia and proinflammatory gene expression are altered by alcohol treatment of rodents and in post-mortem human brain of alcohol use disorder (AUD). In this study we extended previous studies to better characterize microglia in AUD cortex using immunohistochemical (IHC) assessment of cellular proteins and PCR determination of microglial gene mRNA. Interestingly, microglial markers showed increases in expression in AUD patients, although not all showed increases in both IHC staining and mRNA. The microglial marker genes Iba-1, P2RY12 and CD68 showed significant increases in staining in

AUD compared to controls, but no change in mRNA (Aif1, P2ry12, CD68). The resting microglial marker TMEM119 was decreased in AUD brain, both staining and mRNA. Microglial priming marker CD11b was increases in AUD, both staining (MAC1, OX42) and mRNA (CD11b) suggesting AUD microglia are sensitized to proinflammatory activation. CCR2, a monocyte-microglial receptor, showed increases in both cell numbers by IHC as well as mRNA consistent with migration of monocytes into AUD brain. TREM2, Dap12, IL15, and C1q were not different between controls and AUD. These studies are consistent with proinflammatory priming of microglia in AUD increasing oxidative stress which we assessed using the DNA oxidation marker 8-OHdG+IHC. We found 8-OHdG increased with age in both controls and AUD, with AUD showing higher levels across the ages studied. These findings support ethanol priming of microglia to proinflammatory-oxidative stress phenotypes in AUD cortex that are reflected in increased levels of 8-OHdG, a marker of DNA oxidative damage. Priming of microglia likely contributes to AUD neuropathology.

Disclosures: L. Qin: None. **R.P. Vetreno:** None. **L.G. Coleman:** None. **F.T. Crews:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.17/D2

Topic: B.09. Glial Mechanisms

Title: Senescent glial cells drive NMO pathogenesis

Authors: *Y. ZHU[1], L.-J. WU[2], V. A. LENNON[3], T. CHEN[2], F. QI[2];
[1]Physiol. and Biomed. Engin., [3]Neuroimmunology Laboratory, Dept. of Lab. Med. & Pathology, [2]Mayo Clin., Rochester, MN

Abstract: Neuromyelitis Optica (NMO) is a debilitating autoimmune disorder characterized by severe visual loss and paralysis. Effective treatments for NMO are limited, highlighting the need to understand the underlying mechanisms driving its development. Cellular senescence, a stable cell cycle arrest triggered by external stresses, has recently emerged as a potential contributor to various neurological disorders. Senescent cells secrete a range of inflammatory molecules known as the senescence-associated secretory phenotype (SASP), which can impact neighboring cells, alter tissue microenvironments, and induce dysfunction. In the previous study, we have established a mouse model of NMO by infusing either IgG from pooled NMO patients' serum or AQP4-specific monoclonal IgG into the spinal subarachnoid space of mice without exogenous complement. The detailed mechanisms are yet to be determined. To begin exploring the underlying mechanisms, we utilized mass cytometry (CyTOF) for single-cell proteomic analysis of cellular and molecular changes in NMO pathology. We found an accumulation of senescent glial cells, specifically astrocytes and microglia, in the progression of NMO in mice, suggesting their crucial role in the disease pathology potentially triggered by Aquaporin 4 depletion due to IgG binding. Furthermore, we observed a direct correlation between the increased population of

these senescent cells, known for their inflammatory properties, and the prevalence of immune cells in the spinal cords of the NMO mice models, as well as an inverse relationship with the loss of oligodendrocytes. Collectively, our study indicates a novel mechanism that senescent astrocytes activate microglia, instigating microglial senescence, which subsequently promotes immune cell infiltration and oligodendrocyte loss. By elucidating the interplay between senescent glial cells and NMO, this study aims to identify potential therapeutic targets for the treatment of NMO, with broader implications for autoimmune neurological disorders.

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Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR253.18/D3

Topic: B.09. Glial Mechanisms

Support: a grant from the Japan Agency for Medical Research and Development (AMED) Grant 22gk0110060h0001 and 23gk0110060h0002

Title: Lox-1 mediates inflammatory activation of microglia through the p38-mapk/nf-κb pathways under hypoxic-ischemic condition

Authors: *M. ITOH[1], Y. AOKI[2];
[1]Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [2]Pediatrics, Univ. of Miyazaki, Miyazaki-shi Kiyotake-cho Kihara, Japan

Abstract: Background and aim Microglial cells play an important role in the immune system in the brain. Activated microglial cells are not only injurious but also neuroprotective. We confirmed marked lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression in microglial cells in pathological lesions in the neonatal hypoxic-ischemic encephalopathy (nHIE) model brain. Here, we investigated a novel role of LOX-1 and the molecular mechanism of LOX-1 gene transcription microglial cells under hypoxic and ischemic conditions. **Methods** We isolated primary rat microglial cells from 3-day-old rat brains. We treated primary rat microglial cells with oxygen glucose deprivation (OGD) as an in vitro model of nHIE. Then, we evaluated the expression levels of LOX-1, cytokines and chemokines in cells treated with or without siRNA and inhibitors. We performed a luciferase reporter assay and chromatin immunoprecipitation assay. In addition, we analyzed reactive oxygen species and cell viability. **Results** We found that OGD treatment induced LOX-1 expression and inflammatory mediators, such as the cytokines of IL-1β, IL-6 and TNF-α and the chemokines of CCL2, CCL5 and CCL3. Then, the LOX-1 signal transduction pathway was blocked by some inhibitors suppressed the production of inflammatory mediators. We found that NF-κB and HIF-1α bind to the promoter region of the *OLR-1* gene. Moreover, we demonstrated that LOX-1 in microglial cells was autonomously overexpressed by positive feedback of the intracellular LOX-1 pathway.

Conclusion The hypoxic/ischemic conditions of microglial cells induced LOX-1 expression and activated the immune system. LOX-1 and its related molecules or chemicals may be major therapeutic candidates.

Disclosures: M. Itoh: None. **Y. Aoki:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

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Topic: B.09. Glial Mechanisms

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Bright Focus Foundation A2022006F
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
NIH/NIA RF1AG068281

Title: A unique population of senescent microglia in neurodegeneration

Authors: *V. DURAN LAFORET, T. E. FAUST, C. HUNG, R. M. BEITER, D. P. SCHAFER;
Univ. of Massachusetts Chan Med. Sch., Worcester, MA

Abstract: Senescence is a physiological process, which has historically been associated with aging and an inability to undergo cell division. At the same time, senescent cells enter a chronic inflammatory state, which includes secretion of the senescence-associated secretory phenotype or SASP, a cocktail of secreted inflammatory mediators (cytokines, matrix metalloproteases, etc.), which impacts the function of surrounding cells. In addition to aging, recent evidence now implicates senescent cells in neurodegeneration in diseases such as Alzheimer's Disease and Multiple Sclerosis. However, it remains to be determined where these senescent cells are localized in the brain during neurodegeneration and whether senescence influences the molecular phenotype of these cells. We are now using MERFISH (multiplexed error robust fluorescence in situ hybridization), an innovative spatial transcriptomic technique to measure the copy number and spatial distribution of 100's of senescence-related genes directly in human and mouse brain tissue. In the process, we have identified that the distribution of senescence cells is highest in Alzheimer's disease-relevant neurodegeneration vs. normal aging or acute neuroinflammation. Further, of the cell types that have this senescent signature, microglia are the most pronounced. We are now working towards identifying senescence-related secreted factors from microglia that influence neurodegeneration.

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Poster

PSTR253. Microglia: Disease Mechanisms

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Program #/Poster #: PSTR253.20/D5

Topic: B.09. Glial Mechanisms

Support: NIH Grant 5R01AG075897-02
BrightFocus Foundation Grant A2021036S

Title: Investigating the effects of early-life programming on neurodegenerative disease risk

Authors: *P. R. KELLER[1], B. T. CASALI[2], E. G. REED[2];
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Abstract: Microglia, the brain's resident immune cells, participate in a variety of processes such as synaptic pruning and axon growth cone guidance during neurodevelopment, as well as brain sexualization, resulting in adult sexual behaviors. While the male microglial transcriptome assumes a short-lived, pro-inflammatory phenotype in response to a neonatal surge of estradiol (E2), female microglia exhibit persistent inflammatory gene expression beginning in early adolescence. This sustained inflammatory state may be linked to the female bias of neurodegenerative diseases. The current study investigates neonatal E2 exposure in specifying the microglial-mediated response to neurodegenerative disease processes in 5xFAD mice. Utilizing a previously established neonatal E2 administration paradigm, we masculinized female 5xFAD mice, and evaluated changes in the microglial transcriptome using qPCR.

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Poster

PSTR253. Microglia: Disease Mechanisms

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Topic: B.09. Glial Mechanisms

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NIH Grant P20GM121176

Title: Elucidating the role of NFκB in inflammasome-mediated microglial inflammation

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Abstract: Amyloid-β plaques and tau neurofibrillary tangles are the primary pathological components of Alzheimer's dementia (AD). Neuroinflammation has recently been implicated as another key driver of pathology in AD and occurs in response to these danger-associated molecular patterns. Microglia, the innate immune cells of the brain, assemble a multiprotein complex called the inflammasome composed of the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3); the apoptosis-associated speck-like protein containing a CARD (ASC); and inflammatory caspase-1. Oligomerization of ASC and pro-caspase-1 leads to the activation of caspase-1, which can facilitate the cleavage of interleukin-1β (IL-1β) and IL-18. This "ASC-speck" is secreted into the extracellular space and is capable of cross-seeding amyloid-β in a prion-like fashion and contributing to an inflammatory milieu that worsens tau and amyloid-β pathology. Our preliminary studies indicate that ASC-specks also serve as a danger signal; ASC-specks stimulate the release of chemokines and cytokines such as TNFα, IL6, and CXCL1 in primary murine microglia. However, the pathway responsible for the release of these proteins is unknown. Due to previous work related to ASC-specks in the peripheral immune system, we hypothesized that the nuclear translocation of NFκB stimulates the release of proinflammatory chemokines and cytokines in the presence of ASC-specks. C20 immortalized human microglia and BV2 immortalized murine microglia were stimulated with purified ASC-specks and the nuclear translocation of NFκB was compared and evaluated in both human and murine immortalized cell lines through the use of immunocytochemistry and CX7 Cellomics High Content Screening. The release of proinflammatory cytokines and chemokines involved in inflammasome maturation such as IL-1β and IL-18 were evaluated using ELISA. We will report our findings indicating that externally released ASC-specks induce an inflammatory response in microglia. This study provides key insights into how the ASC-speck serves as a danger signal to drive neuroinflammatory processes involved in AD pathology.

Disclosures: K. Sanchez: None. **J. Hulse:** None. **G.A. Rosenberg:** None. **K. Bhaskar:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.22/D7

Topic: B.09. Glial Mechanisms

Support: NIAID Grant R15 Area Award R15AI156879
NE-INBRE NIGMS 5P20GM1033427

Title: Mediation of IRF7 transcriptional regulation through a novel long non-coding RNA

Authors: *S. CIECHANOWSKI[1], N. MATHY[4], O. BURLEIGH[2], X.-M. CHEN[5], K. DRESCHER[3], A. SHIBATA[2];

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Abstract: Systemic immune responses due to viral infection significantly contribute to the neurodegeneration seen in various diseases. Microglia participate in antiviral immune responses and promote both neurorecovery and neurotoxicity. Long noncoding RNAs (lncRNAs) are transcripts that lack coding potential and perform regulatory activities through interactions with RNA-binding proteins, such as transcription factors. Our previous work shows that lncRNAs can regulate microglial antibacterial responses, so we hypothesize that lncRNAs are also important in microglial antiviral immunity. In vivo and in vitro FBV/nJ mouse systems were used to study whether Theiler's murine encephalomyelitis virus (TMEV) altered lncRNA expression in microglia. Post-TMEV infection, lncRNA Nostrill expression significantly increases 3.9 ± 0.8fold in TMEV-infected and chronically demyelinated brain, 3.0 ± 0.04fold in infected primary microglia, and 2.8 ± 0.1fold in infected microglial cell lines, compared to uninfected controls (n=3, ±=SEM, $p<0.05$). Upregulation of Nostrill in response to TMEV is dependent upon NFκB signaling, as NFκB inhibitors block TMEV upregulation of Nostrill. TMEV-mediated NFκB signaling significantly upregulates gene transcription of interferon response factor 7 (IRF7) to ~22fold in primary microglia and to ~14fold in microglial cell lines as compared to unstimulated controls (n=3, $p<0.05$). Silencing of Nostrill using siRNA constructs blocks upregulation of IRF7 following infection of microglial cell lines with TMEV. Overexpression of Nostrill significantly increases IRF7 gene transcription without (~2fold) or with (~8fold) TMEV infection, as compared to controls (n=3, $p<0.05$). Following TMEV infection in microglial cell lines, qRT-PCR analysis showed an increase in infection burden with silencing of Nostrill (2.7 ± 0.3fold), and a reduced viral burden with the over expression of Nostrill (0.4 ± 0.1fold), as compared to control (n=3, ±=SEM, $p<0.05$). Nostrill has also been shown to bind to the p65 subunit of NFκB by RIP. ChIP analyses suggest that Nostrill targets p65 to promoter regions of IRF7. These data indicate that viral-induced upregulation of Nostrill is necessary and sufficient for regulation of IRF7 gene transcription and IRF7-related microglial antiviral immune responses. An increased understanding of the regulatory factors of microglial antiviral activity is critical for understanding immune responses in the CNS that contribute to neurodegeneration.

Disclosures: S. Ciechanowski: None. **N. Mathy:** None. **O. Burleigh:** None. **X. Chen:** None. **K. Drescher:** None. **A. Shibata:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.23/D8

Topic: B.09. Glial Mechanisms

Support: olorado Department of Public Health and Environment; Contract IHEA 140802

Title: Novel spatial quantification showed glial-neuron interaction after TBI

Authors: *T. GREEN[1], L. BEAUREGARD[1], S. MURPHY[2], M. OPP[1], R. ROWE[1];
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Abstract: Introduction: Traumatic brain injury (TBI) causes dysfunction of orexin/hypocretin neurons, which contributes to post-traumatic sleep-wake disturbances. Injury-induced glial activation in proximity to orexin neurons may exacerbate dysfunction and promote neuronal apoptosis. Using a modified Sholl analysis, we investigated spatial relationships among hypothalamic orexin neurons, microglia, and astrocytes, and hypothesized that activated microglia and astrocytes would surround orexin neuronal cell somas following focal TBI. Methods: Mice received a controlled cortical impact (depth -1 mm) or sham surgery. At 3 days post-injury, brains were harvested, cryosectioned, and co-labeled for orexin neurons, astrocytes, and microglia. Z-stacked images were taken spanning the lateral hypothalamus. Concentric rings were placed on approximately 3 neurons per image (n=127 neurons), spanning 50µm from the soma center, in 3µm increments. The number of intersections on concentric rings surrounding the neuron were recorded for both microglia and astrocytes. This approach showed the proximity of glia to the orexin neuron soma. Nearest-neighbor glial morphology measurements are ongoing. Results: After TBI, as the frequency of microglial intersections proximal to the neuron increased, astrocyte intersections also increased both contralateral ($p=0.020$) and ipsilateral ($p=0.025$) to the injury. Astrocytes were further from orexin neurons compared to shams in the contralateral hypothalamus, ($p=0.029$) and in the ipsilateral hypothalamus ($p=0.004$). In the ipsilateral hemisphere, where neuropathology is routinely observed, astrocytes were closer to orexin neurons after TBI. Conclusions: Our results indicate an increased localization of astrocytes to orexin neurons after TBI. We demonstrate a novel Sholl analysis modification for examining the spatial relationships between any cell types in biological tissue.

Disclosures: T. Green: None. **L. Beauregard:** None. **S. Murphy:** None. **M. Opp:** None. **R. Rowe:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.24/D9

Topic: B.09. Glial Mechanisms

Support: College of Pharmacy of the University of Minnesota

Title: Agmatine modulates microglial activity in nucleus accumbens of fentanyl self-administration mice

Authors: *C. BARAJAS[1], C. PETERSON[2], K. F. KITTO[1], G. L. WILCOX[4], C. A. FAIRBANKS[3];

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Abstract: Chronic pain affects a significant fraction of the world population and is one of the major contributors to the global burden of disease. Opioid medications are commonly prescribed for the treatment of pain but carry high risk for addiction and overdose. Therefore, development of new medications with reduced risk of addiction and opioid use disorder is a high national priority. It is well established that the neuroplastic changes underlying chronic pain and addiction are dependent on activation of the N-methyl-D-aspartate (NMDA) receptor. Microglia also contribute to this neuroplasticity through interactions with neurons in CNS areas implicated in reward, such as the nucleus accumbens (NAc), and pain, such as the spinal cord. The decarboxylated form of L-arginine, agmatine, antagonizes the NMDA receptor and inhibits NMDA-evoked current, behavior, and NO production. Agmatine also inhibits the development of chronic pain and manifestations of chronic opioid exposure, but without the associated motor toxicity commonly observed with NMDA receptor antagonists. Therefore, agmatine-based therapeutics could provide an effective therapy for pain or opioid addiction with potentially limited side effects. Despite the potential of agmatine as a therapeutic, it is not yet clear whether the actions of agmatine on pain and reward circuitry involve microglia. To evaluate the effects of agmatine on microglia reward circuit remodeling, female ICR mice (21-30g) were separated into experimental groups and were able to press either for oral fentanyl reward (10 ug/mL) or inactive control over 12 hours of nightly access. Prior to each session, mice were treated (i.p.) with either agmatine (30 mg/kg) or saline. Agmatine-treated subjects had significantly decreased responding as compared to their saline controls. Brains were collected and immunohistochemical staining for Iba1, a microglial marker, in the NAc was conducted. Initial analysis demonstrated distinct morphological identities of microglia in NAc of mice treated with agmatine vs. those treated with saline. Saline-treated mice had increased microglia in the activated amoeba form compared to agmatine-treated mice. In contrast, agmatine-treated mice had increased microglia in the resting ramified form. These exploratory data suggest that agmatine may prevent neuroplastic remodeling through anti-inflammatory mechanisms.

Disclosures: C. Barajas: None. **C. Peterson:** None. **K.F. Kitto:** None. **G.L. Wilcox:** None. **C.A. Fairbanks:** None.

Poster

PSTR253. Microglia: Disease Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.25/D10

Topic: B.10. Demyelinating Disorders

Support: SJBSM Competitive Research Pilot Projects Program YIN-2019

Title: Endothelin-1 as an Activator of Pro-Inflammatory Microglia cells in MS

Authors: *S. BOU ROLON[1], J. ALVARADO[1], D. CAPO[1,2], J. P. MOLIERE[1], C. P. ARENAS[1], Y. INOSTROZA-NIEVES[1];
[1]San Juan Bautista Sch. of Med., Caguas, Puerto Rico; [2]Univ. Autonoma de Guadalajara, Mexico, Mexico

Abstract: Endothelin-1 as an Activator of Pro-inflammatory Microglia Cells in Multiple Sclerosis Shakira Bou, José Alvarado, Diego Capo, Jean P. Moliere, Claudia P. Arenas and Yaritza Inostroza-Nieves

Abstract

Objective: Demonstrate that high levels of ET-1 contribute to the progression of MS by studying the activation of microglia cells *in vitro*.

Background: Multiple sclerosis (MS) is a neurodegenerative autoimmune disease characterized by inflammation, demyelination, and axonal degeneration. In MS patients, demyelination is associated with activated microglia, which are the resident innate immune cells of the central nervous system and play an important role in inflammatory responses. ET-1 is a potent vasoconstrictor that has been documented in MS by inducing severe and prolonged cerebral vasoconstriction. However, the mechanism of how ET-1 activates a proinflammatory response is unknown.

Methods: To study ET-1 levels in MS, we used C57BL/6 mice with or without induced experimental autoimmune encephalomyelitis (EAE), and the score history was taken. The brain ET-1, TNF, and iNOS levels were measured by qPCR and ELISA. To investigate ET-1's role in microglia activation, HMC3 cells were treated with ET-1 in the presence or absence of endothelin receptor B (ETRB) antagonist, BQ788. TNF levels were measured using ELISA. Nitric Oxide (NO) production was measured using Griess Reagent. ROS production was measured using the MUSE Oxidative Stress kit.

Results: We found that the ET-1 gene and protein were upregulated by 1.5 folds (±0.4, $p<0.05$) in EAE mice compared to the control. ET-1 levels were correlated with EAE score at onset ($R2 = 0.9282$, $p<0.05$). In addition, TNF and iNOS were upregulated by 4.6 folds and 3.8 folds in EAE mice, respectively. TNF levels were correlated with ET-1 levels ($R2 = 0.3760$, $p<0.05$). Moreover, ET-1 increases TNF levels by 90% ($p<0.05$) in HMC3 cells, and it was decreased to basal levels in the presence of the ETRB antagonist. iNOS, NO, and ROS production are induced by ET-1 ($p<0.05$), and treatment with the ETRB antagonist was able to decrease them ($p<0.05$).

Conclusion: These data suggest that *in vitro* administration of ET-1 was able to activate microglia, increasing significantly inflammatory cytokines levels and NO and ROS formation. This is a novel mechanism of microglial cell activation and will provide key information to understand MS pathogenesis.

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Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.01/D11

Topic: B.10. Demyelinating Disorders

Support: NIH Grant NS102196
NIH Grant NS124707
KSCHIRT 16-1
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NIH Grant AG033649
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NIH Grant T32AG057461

Title: Rit1 deficiency alters cerebral lipid metabolism and reduces white matter tract oligodendrocytes and conduction velocities

Authors: *D. ANDRES[1], L. WU[2], F. WANG[2], C. MONCMAN[2], M. PANDEY[2], H. CLARKE[2], H. FRAZIER[2], L. YOUNG[2], M. GENTRY[2], W. CAI[3], O. THIBAULT[2], R. SUN[2];
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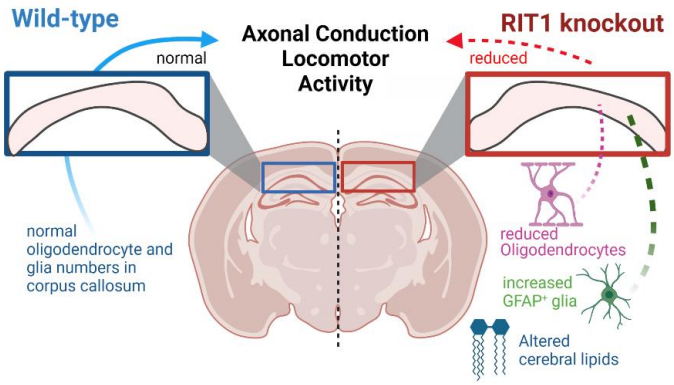
Abstract: Oligodendrocytes (OLs) generate lipid-rich myelin membranes that wrap axons to enable efficient transmission of electrical impulses. Using a *RIT1* knockout mouse model and *in situ* high-resolution matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) coupled with MS-based lipidomic analysis to determine the contribution of RIT1 to lipid homeostasis. Here, we report that RIT1 loss is associated with altered lipid levels in the central nervous system (CNS), including myelin-associated lipids within the corpus callosum (CC). Perturbed lipid metabolism was correlated with reduced numbers of OLs, but increased numbers of $GFAP^+$ glia, in the CC, but not in grey matter. This was accompanied by reduced myelin protein expression and axonal conduction deficits. Behavioral analyses revealed significant changes in voluntary locomotor activity and anxiety-like behavior in $RIT1^{KO}$ mice. Together, these data reveal an unexpected role for RIT1 in the regulation of cerebral lipid metabolism, which coincide with altered white matter tract oligodendrocyte levels, reduced axonal conduction velocity, and behavioral abnormalities in the CNS.



Disclosures: **D. Andres:** None. **L. Wu:** None. **F. Wang:** None. **C. Moncman:** None. **M. Pandey:** None. **H. Clarke:** None. **H. Frazier:** None. **L. Young:** None. **M. Gentry:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Maze Therapeutics, Valerion Therapeutics, Ionis Pharmaceuticals. F. Consulting Fees (e.g., advisory boards); Maze Therapeutics, PTC Therapeutics, Glut1-DEficiency Syndrome Foundation. **W. Cai:** None. **O. Thibault:** None. **R. Sun:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Maze Therapeutics. F. Consulting Fees (e.g., advisory boards); Maze Therapeutics.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.02/D12

Topic: B.10. Demyelinating Disorders

Support: The Legacy of Angels Foundation

Title: Galactosylceramidase deficiency and pathological abnormalities in cerebral white matter of Krabbe Disease

Authors: D. IACONO[1,2], S. KOGA[3], H. PENG[1,2], J. DAIKER[4], A. R. HERDT[1,2], M. H. GELB[4], D. W. DICKSON[3], ***C. W. LEE**[1,2];

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Abstract: Krabbe Disease (KD) is an autosomal recessive disorder resulting from loss-of-function mutations in the *GALC* gene. Functional deficiency of galactosylceramidase (GALC) leads to progressive demyelination in the nervous systems. Psychosine, which can only be degraded by GALC, is a key player in pathologic cascades. Despite the central role of GALC in KD pathomechanism, investigations of GALC protein deficiency are largely absent, due in part, to the lack of sensitive antibodies available. Leveraging custom antibodies that can detect endogenous GALC, we demonstrated that GALC was predominantly localized to oligodendrocytes in cerebral white matter of infant brain. Mature GALC was also quantitatively detected by western blot and correlated to enzyme activity. The common p.Ile562Thr polymorphic variant was associated with reduced mature GALC protein and activity. In three infantile KD brains, homozygous null mutations led to deficiency in total GALC protein and activity. Interestingly, although GALC activity was absent, normal levels of total GALC protein were detected in a later-onset KD brain using our custom ELISA, which suggests its potential use in KD prognosis. Among the infantile KD brains, we quantified a 5-fold increase in psychosine levels, and also a marked increase in acid ceramidase and hyperglycosylated LAMP1 levels in periventricular white matter, a major pathological site, when compared with age-matched normal controls. While near complete demyelination was observed in the infantile KD brains, we quantified that an early-infantile case (10 months) had about 3-fold increase in both CD68-positive globoid cells and CD8-positive T lymphocytes in the white matter, compared with a slower progressing infantile case (21 months). The results suggest a positive correlation between clinical severity and neuropathology. Overall, our findings have advanced the understanding of GALC protein biology in the context of normal and KD brain white matter. We also revealed neuropathological changes that may provide insights to understand KD pathogenesis.

Disclosures: D. Iacono: None. **S. Koga:** None. **H. Peng:** None. **J. Daiker:** None. **A.R. Herdt:** None. **M.H. Gelb:** None. **D.W. Dickson:** None. **C.W. Lee:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.03/D13

Topic: B.10. Demyelinating Disorders

Support: European Research Council (ERC) under the European Union's Horizon Europe research and innovation programme (grant agreement No. 101044180).

Title: The correlation between in-vitro conduction velocities and myelination provide insights into the role of myelin in nerve signal transmission

Authors: *H. VILA-MERKLE[1], N. W. HANSEN[2], J.-F. PERRIER[2], T. DYRBY[3,1];
[1]Copenhagen Univ. Hosp. Amager and Hvidovre, Hvidovre, Denmark; [2]Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark; [3]Dept. of Applied Mathematics and Computer Sci., Tech. Univ. of Denmark, Kongens Lyngby, Denmark

Abstract: Background: The timely and accurate delivery of information is vital for the proper functioning of the nervous system. This directly depends on the regulation of neuronal conduction velocity, which is necessary to ensure the precise execution of motor skills, sensory integration, and cognitive functions. In vertebrates, rapid signal transmission along nerve fibers is made possible by the myelination of axons. However, alterations in myelin integrity can lead to changes in conduction. To date, the specific mechanisms underlying the systematic regulation of conduction velocity and its relationship with myelin alterations remains poorly understood. The objective of this study was to investigate how acute hypoxia affects action potential conduction in a brain slice preparation, and if these changes are associated with alterations of myelin integrity. Methods: In this study, we used in-vitro extracellular recordings of evoked compound action potentials in mice brain slices to investigate the impact of hypoxia on axonal conduction velocity along the corpus callosum. Additionally, electron microscopy images were collected on the same tissue to correlate the myelin layer structure in relation to function of the hypoxia-induced alterations. Results: After 5 minutes, the hypoxic condition elicited notable alterations in the conduction velocity, as evidenced by changes observed in both the amplitude and latency of evoked potentials following electrical stimulation of the corpus callosum. The observed effects primarily targeted myelinated axons, as evidenced by a distinct shift in conduction velocity alterations favoring a worsening trend in myelinated axons compared to unmyelinated axons. Furthermore, preliminary electron microscopy evidence suggests the presence of alterations, such as loosening, in the myelin layer. However, it is important to consider that further investigations will determine whether the observed myelin alterations was indeed caused by the acute hypoxia. Discussion: In this study, we demonstrate a reduction in conduction velocity among a cohort of myelinated axons, which could be indeed caused by the loosening of myelin due to exposure to hypoxia.

Disclosures: H. Vila-Merkle: None. **N.W. Hansen:** None. **J. Perrier:** None. **T. Dyrby:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.04/D14

Topic: B.10. Demyelinating Disorders

Title: Correlated structural and functional deficits in a mouse model of demyelination

Authors: *A. DAS[1], J. BOROVICKA[1], J. ICARDI[1], P. AGOCHIYA[1], S. SINGH[1], J. MANWORREN[1], H. DANA[1,2];

[1]Neurosciences, Lerner Res. Inst., Cleveland, OH; [2]Dept. of Mol. Medicine, Sch. of Med., Cleveland Clin. Lerner Col. of Medicine, Case Western Reserve Univ., Cleveland, OH

Abstract: Damage to the myelin sheath that protects axons in the central nervous system (CNS) is a hallmark of inflammatory demyelinating diseases such as multiple sclerosis (MS). Cuprizone-induced demyelination in rodents is a widely used model for studying demyelination, remyelination, and related changes in the brain tissue. Cuprizone is a copper chelator, which when added to a rodent's regular diet induces death of mature oligodendrocytes and subsequent demyelination of the CNS. We previously showed that neuronal firing rate is decreased in CA1 and DG areas of the mouse hippocampus within several days following cuprizone ingestion and remains low for multiple weeks. Here, we added longitudinal, label-free monitoring of myelin using third-harmonic generation (THG) in parallel to monitoring of neuronal firing patterns in the same mice and monitoring potential differences between male and female mice. Our data suggest a link between the functional and structural deficits in the mouse hippocampus caused by cuprizone-induced demyelination. Using this integrated structural-functional recording approach, we identified that functional loss of neuronal activity and structural loss of myelin showed a trend towards correlation, but that the functional deficits were apparent much earlier than myelin loss. We also found trends toward functional, but not structural, sex differences, where neuronal firing rates of female mice were decreased more severely during the cuprizone-induced demyelination period than these of males. In summary, the application of nonlinear microscopy methods enables longitudinal detection of same-subject demyelination-related deficits, as well as the ability to link deficit progression with brain function, thereby facilitating a new approach to test the efficacy of neuroprotective treatments and how they may modulate or preserve brain circuits.

Disclosures: A. Das: None. **J. Borovicka:** None. **J. Icardi:** None. **P. Agochiya:** None. **S. Singh:** None. **J. Manworren:** None. **H. Dana:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.05/D15

Topic: B.10. Demyelinating Disorders

Support: T32 Grant 5T32NS099042-20
NIH Grant R01NS125230
NIH Grant R01NS115975

Title: Oligodendrocyte precursor cell survival after differentiation increases with quiescence depth and following demyelination

Authors: *M. STOCKTON, E. HUGHES;
Cell and Developmental Biol., Univ. of Colorado, Anschutz Med. Neurosci. Grad. Training Program, Aurora, CO

Abstract: Oligodendrocytes are the myelin-forming cells of the central nervous system. New oligodendrocytes are produced throughout life from oligodendrocyte precursor cells (OPCs) in a process called oligodendrogenesis. Oligodendrogenesis is an inefficient process; most differentiating OPCs die before they generate myelinating oligodendrocytes. In demyelinating diseases, decreased oligodendrogenesis is thought to underlie limited regeneration. However, it remains unclear whether this deficiency is due to inhibited OPC differentiation or reduced survival of OPCs after differentiation. Furthermore, emerging evidence suggests OPCs have functionally distinct populations. Here, we aim to understand the factors and the functional consequences of OPC heterogeneity in health and disease.
To explore OPC heterogeneity, we use longitudinal *in vivo* 2-photon imaging under healthy conditions in young adult mice. Using a "real-time" fate mapping approach (*Olig2-CreER;R26-lsl-tdTom;MOBP-eGFP mice*), we determined proliferation, differentiation, and oligodendrogenesis for individual OPCs over 12 weeks (n=136-197 OPCs / mouse). By examining cell-cycle length for each OPC, we found a subset that existed in a non-proliferative state of quiescence. Therefore, we subdivided the OPC population into 3 groups according to the depth of quiescence: Active OPCs (0-7 days since last division), shallowly quiescent OPCs (8-42 days since last division), and deeply quiescent OPCs (43+ days since last division) to explore functional heterogeneity. In healthy mice, we found that survival after differentiation was higher for deeply quiescent OPCs (47.7±2.2%) compared to shallowly quiescent (14.0±2.3%) and active OPCs (0.0±0.0%). Next, we investigated OPC behaviors following demyelination injury induced by acute cuprizone treatment (0.2% cuprizone diet for 3 weeks; n=4). Two weeks after demyelination, the daily rate of OPC differentiation (1.8±0.1%) was not altered compared to the healthy mice (1.2±0.2%). However, the survival of OPCs after differentiation was increased in cuprizone treated (56.1±9.1%) compared to healthy mice (13.8±5.9%). Survival after differentiation was higher for deeply quiescent OPCs (75.5±9.2%), compared to both shallowly quiescent (42.6±3.2%) and active (3.1±3.1%) OPCs in the demyelinated mice. Finally, we found that the pool of deeply quiescent OPCs produced 58±6.3% of the new oligodendrocytes during remyelination despite only making up 23.6±2.2% of the total OPC population. Together, these data suggest that deeply quiescent OPCs may be a functionally distinct population in the healthy and remyelinating brain.

Disclosures: M. Stockton: None. **E. Hughes:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.06/D16

Topic: B.10. Demyelinating Disorders

Support: MOST 111-2320-B-A-49-011-MY3
MOST 109-2320-B-010-027-MY3

Title: Asic3 delay nerve regeneration process to prolong mechanical allodynia

Authors: *J.-Y. HSU, W.-H. SUN;
Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: ASIC3 delay nerve regeneration process to prolong mechanical allodynia Jia-Yun Hsu [1] and Wei-Hsin Sun [1,2*1] Program in Molecular Medicine, College of Life Sciences, National Yang Ming Chiao TungUniversity, Taipei 112, Taiwan[2] Department of Life Sciences and Institute of Genome Sciences, National Yang Ming Chiao TungUniversity, Taipei 112, TaiwanNeuropathic pain is triggered by lesions on peripheral or central nervous systemwhich caused spontaneous and abnormal pain sensation, and approximately 7% of theglobal population is affected with long-term physical and mental health condition.Wallerian degeneration as a factor involved in nerve injury-induced pain sensation,including axonal degeneration and Schwann cell degradation. Previous studies haveshown that delayed sciatic nerve degeneration postpones chronic constriction injury(CCI)-induced pain and sciatic nerve regeneration reverses pain. Acid-sensing ionchannel 3 (ASIC3), a proton-gated cation channel, is involved in mechanical allodyniainduced by nerve injury and inflammation. We previously demonstrated that *Asic3*$^{-/-}$mice have less loss of dorsal root ganglion neurons at week 1 post CCI surgery andmore small neuron regeneration at week 8 by lowering M1/M2 ratio on sciatic nerve,which contributes to the relief of mechanical allodynia from week 8. However, theunderlying mechanism for ASIC3-mediated nerve degeneration to relieve pain is stillunclear. We performed CCI on the sciatic nerve as a model of neuropathic pain toexamine temporal changes of the nerve. Here, we found that nerve degeneration beganfrom the injury site to distal stump and then to proximal stump on sciatic nerve, whilethe regenerative process was started from the proximal stump through the injury site todistal stump in CCI mice. Histological analysis of axons reveals that nerve regenerativephase includes two sequential stages: stage I, medium-diameter fiber regeneration andstage II, large-diameter fiber regeneration. ASIC3 deletion slightly slowed down thedegeneration process but facilitated the regeneration process to stage II. The earlyregeneration could partially contribute to the shortening of CCI-induced mechanicalallodynia in *Asic3*$^{-/-}$ mice. Accordingly, ASIC3 modulation on the regeneration processof the sciatic nerve could be critical to the maintenance of mechanical allodynia afternerve injury.

Disclosures: J. Hsu: None. **W. Sun:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.07/D17

Topic: B.10. Demyelinating Disorders

Support: BC Children's Hospital Research Institute Investigator Grant Award (IGAP)
Michael Smith Health Research BC Scholar Award
Rare Diseases: Models and Mechanism Network
BC Children's Hospital Foundation
BC Graduate Scholarship

Title: Development of cellular models to explore the pathogenesis of claudin-11-mediated hypomyelinating leukodystrophy

Authors: *S. C. GJERVAN[1,2], O. OZGOREN[1,2], L. HENRY[1,2], A. WU[1,2], C. MCCAMUS[1,2], M. POLOZ[1,2], J. BEGIN[1,2], S. STOCKLER[2,3], M. A. POULADI[1,2];
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Abstract: Leukodystrophies are a group of genetic diseases that affect the white matter of the central nervous system (CNS). Clinical presentations are variable with over fifty genetic causes identified to date. *De novo* heterozygous stoploss mutations in *CLDN11,* the gene encoding the myelin tight junction protein claudin-11, have recently been identified as the cause of an early-onset neurodegenerative disease termed hypomyelinating leukodystrophy 22 (HLD22). How such mutations in *CLDN11* cause HLD22 is not well understood. To elucidate the pathogenic mechanisms involved, we first established immortalized cell lines with stable expression of wild-type (WT) or mutant (MT) claudin-11. Western blot analysis showed that the stoploss mutation results in the elongation and reduced stability of MT claudin-11. Furthermore, immunofluorescence imaging showed markedly reduced surface abundance of MT claudin-11 relative to WT. Using bafilomycin A1 and lactacystin treatments, we demonstrate that the reduced expression of MT claudin-11 reflects increased clearance through lysosomal and proteasomal pathways. As endoplasmic reticulum (ER) stress has been implicated in the pathogenesis of a number of myelinopathies, we evaluated the response of the immortalized MT and WT claudin-11 cell lines to ER stressors. MT claudin-11 cells showed elevated cell death and reduced viability in response to thapsigargin, suggesting that ER stress may contribute to the pathogenesis of HDL22. Overall, our results to date point to decreased protein stability and increased ER stress as potential mechanisms contributing to the pathogenesis of HLD22.

Disclosures: S.C. Gjervan: None. **O. Ozgoren:** None. **L. Henry:** None. **A. Wu:** None. **C. McCamus:** None. **M. Poloz:** None. **J. Begin:** None. **S. Stockler:** None. **M.A. Pouladi:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.08/D18

Topic: B.10. Demyelinating Disorders

Support: DBT, Govt of India (DBT/PR21413/MED/122/40)

Title: Elucidating the role of the JAK-STAT cell signaling pathway in oligodendrocyte maturation in vitro

Authors: *S. TYAGI[1], V. SHRIVASTAVA[1], D. DEY[1], S. RANI[1], J. B. SHARMA[2], J. K. PALANICHAMY[1], S. SINHA[1], P. SETH[3], S. SEN[1];
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Abstract: Perinatal hypoxic injury in preterm neonates results in neurological deficits. Oligodendrocyte (OL) maturation arrest is usually associated with such deficits. Premyelinating OL predominate in preterm infants, and are particularly vulnerable to hypoxic injury. Understanding the mechanistic pathways of OL development is a prerequisite to developing therapeutic strategies to overcome OL maturation arrest. Analyzing transcriptional datasets (RNA sequencing) in primary OL cells derived from human fetal neural stem cells (FNSCs) revealed the involvement of the JAK-STAT cell signaling pathway in terminal OL maturation. To validate our findings, we used the MO3.13 cell line resembling premyelinating OL, which can be differentiated into mature OL over 7 days, using phorbol 12-myristate 13-acetate (PMA). Morphological changes, increased expression of mature-OL marker MBP (qPCR and ICC) and decreased expression of premyelinating OL markers NG2 and O4 (ICC) confirmed the differentiation of MO3.13 into mature OL (n=5). Flow cytometry indicating increased expression of MBP also confirmed the differentiation (n=3). Upregulation of the ligand IL-6 and the transcription factor STAT3 using ELISA and qPCR respectively, validated the involvement of the JAK-STAT pathway during OL maturation in MO3.13 cells (n=3). Interestingly, while total STAT3 levels remained constant, phosphorylated STAT3 (pY705) levels increased during MO3.13 differentiation, exhibiting the highest expression at day 7, using western blotting (n=3). MO3.13 differentiation was induced using PMA, with and without STAT3 specific inhibitor (Stattic). Flow cytometry demonstrated MBP-positive cells (treated with PMA alone) to be 51% (day 3), 65% (day 5), and 99% (day 7) while they measured 42% (day 3), 46% (day 5), and 49% (day 7) with both PMA and Stattic, thereby confirming the involvement of the JAK-STAT pathway in terminal OL maturation (n=3). Western blotting confirmed an increase in phosphorylated STAT3 (pY705) while total STAT3 remained constant while differentiating MO3.13 with PMA alone (n=3). However, when STAT3 specific inhibitor (Stattic) was added along with PMA, phosphorylated STAT3 (pY705) levels decreased in a time-dependent manner with no expression detected at day 7 (n=3). Morphological changes also confirmed the results. These novel findings highlight the involvement of the JAK-STAT pathway in OL maturation. This may aid in the development of new therapeutic strategies to overcome the OL maturation arrest associated with perinatal hypoxic injury. It may also contribute to developing therapeutics for other demyelinating disorders.

Disclosures: S. Tyagi: None. **V. Shrivastava:** None. **D. Dey:** None. **S. Rani:** None. **J.B. Sharma:** None. **J.K. Palanichamy:** None. **S. Sinha:** None. **P. Seth:** None. **S. Sen:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.09/D19

Topic: B.10. Demyelinating Disorders

Title: Enteric Glial Cells as a possible source of myelin antigen in Inflammatory Bowel Disorders and Multiple Sclerosis

Authors: *R. BROWN, H. LE, A. NIVEN, A. GAULTIER;
Neurosci., The Univ. of Virginia, Charlottesville, VA

Abstract: Multiple Sclerosis (MS) is a chronic neurodegenerative disorder marked by an autoimmune response against myelin in the Central Nervous System (CNS). There is a link between the gut and MS as patients frequently present with gastrointestinal symptoms, suggesting dysregulation of local motility circuits in the Enteric Nervous System (ENS). Further, patients with Inflammatory Bowel Disorders (IBDs) such as Ulcerative Colitis have an increased risk of developing MS. Enteric glial cells (EGCs) are observed throughout the gastrointestinal tract where they are closely associated with immune cells. EGCs are poised to contribute to T cell-mediated intestinal inflammation, as they express antigen presentation machinery and costimulatory molecules. Although the ENS is devoid of conventional myelin sheaths, EGCs express several myelin proteins such as Proteolipoprotein 1 (PLP1) and Myelin Basic Protein (MBP). Further, PLP1 and MBP are major constituents of myelin in the CNS and are targeted by the immune system in MS. As such, autoimmune reactions initiated by EGC antigen presentation could potentially act to trigger CNS autoimmunity in MS. I have demonstrated that EGCs are capable of antigen presentation via MHC I and MHC II in *vitro.* To model IBD and MS comorbidity, I have utilized rodent models of colitis paired with the MS model, Experimental Autoimmune Encephalomyelitis (EAE). I have observed upregulation of MHC I by EGCs in the Dextran Sodium Sulfate colitis model as well as EAE. However, I see little to no MHC II expression by EGCs in either of these models. Ongoing work includes studying how comorbidity of these models affects EGC MHC I/II expression levels and intestinal T cell clones that recognize EGC derived peptides. I am also further characterizing the functional relevance of EGC antigen presentation in disease states by investigating whether disrupting EGC antigen presentation using genetic mouse models will impact disease severity. These results could provide insights into the role of EGCs in the etiology and pathogenesis of IBDs and MS.

Disclosures: R. Brown: None. **H. Le:** None. **A. Niven:** None. **A. Gaultier:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.10/D20

Topic: B.10. Demyelinating Disorders

Support: MS Society USA RG-2203-39395
BC Children's Hospital Foundation
BC Children's Hospital Research Institute Investigator Grant Award (IGAP)
Michael Smith Health Research BC Scholar Award SCH-2020-0656

Title: Functional analysis of putative pathogenic variants in Ermin, a white matter disease-linked myelin protein

Authors: L. HENRY[1], O. K. OZGOREN[2,3,4,5], B. SIM[1], N. M. B. YUSOF[1], ***M. A. POULADI[2,3,4,5];**
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Abstract: Ermin, encoded by the gene *ERMN*, is an actin-binding protein expressed almost exclusively in mature oligodendrocytes, the myelination cells of the central nervous system (CNS). Ermin has been shown to play a role in oligodendrocyte arborisation as well as in maintaining myelin integrity. Mutations predicted to truncate and abrogate Ermin function have been identified in a multi-incident multiple sclerosis (MS) family. Furthermore, we have recently shown that Ermin-deficient mice exhibit a number of myelin abnormalities such as outfolding, fragmentation and altered compaction, as well as increased susceptibility to experimental autoimmune encephalomyelitis, a widely-used model of MS. While nonsense, truncating mutations in *ERMN* are rare, a large number of coding, single-nucleotide variants (SNVs) are substantially more frequent in the general population. In this study, we used *in silico* analyses to identify potentially pathogenic, naturally-occuring SNVs in *ERMN*. We followed this with *in vitro* studies assessing the impact of selected SNVs on Ermin function including measures of cell morphology, expression levels, and actin interactions. Our study uncovered a number of SNVs with marked impact on Ermin-related measures and support further investigation of Ermin variants as a potential risk factor for white matter disorders.

Disclosures: L. Henry: None. **O.K. Ozgoren:** None. **B. Sim:** None. **N.M.B. Yusof:** None. **M.A. Pouladi:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.11/D21

Topic: B.10. Demyelinating Disorders

Support: NIH NINDS (R01NS104021)
Department of Defense CDMRP (W81XWH-21-MSRP-EHDA)

Title: Store-operated calcium entry-dependent signaling in adult OPCs acts to delay oligodendrocyte differentiation following demyelination

Authors: *R. RAVICHANDAR, R. MUTHAIAH, D. SARASWAT, F. GADELKARIM, R. A. SEIDMAN, F. J. SIM;
State Univ. of New York, Univ. at Buffalo, Buffalo, NY

Abstract: One of the hallmarks of multiple sclerosis (MS) is inefficient/failed remyelination that contributes to neurodegeneration. Inhibition of $M_{1/3}R$ in oligodendrocyte progenitor cells (OPCs) promotes differentiation and remyelination. However, the operant downstream mechanisms are poorly understood. $G_{\alpha/q}$ receptor activation triggers endoplasmic reticulum Ca^{2+} release and replenishment via store operated calcium entry (SOCE) modulated by Ca^{2+} sensors, namely STIM1 and STIM2. Our previous gain-of-function studies in human OPCs showed that specific optogenetic activation of SOCE acts to reduce differentiation *in vitro*. As such, we hypothesize that OPC SOCE acts to delay or prevent OPC differentiation and may thereby impair remyelination. In this study, we utilized a tamoxifen inducible cre-lox strategy to conditionally knockout (cKO) SOCE in adult OPCs prior to lysolecithin-induced spinal cord demyelination. *NG2creER;Stim1/2* floxed mice and cre-negative littermates were injected at 8-weeks with tamoxifen. Following demyelination, we analyzed OPC density and proliferation at 5 days post-lesion (dpl). *Stim1* or *Stim2* cKO had no significant effect on the density of $Olig2^+$ cells at 5 dpl and did not alter the proportion of EdU^+ proliferating OPCs. Likewise, the density of $Pdgfra^+$ OPCs was not influenced at 7 dpl. However, at 7 dpl, both *Stim1* and *Stim1/2* cKO mice exhibited increased densities of $CC1^+$ and $Plp1^+$ oligodendrocytes (OLs) as well as increased proportion of $CC1^+$ OLs among the Olig2-defined OL lineage pool (2-way ANOVA, $p < 0.05$). As the individual effects of *Stim2* and the interaction between *Stim1/2* were not significant, these results indicate that *Stim1* alone plays a critical role. Next, to determine whether pharmacological inhibition of SOCE may improve OL differentiation following demyelination, we intraspinally injected a small molecule Orai1 inhibitor CM4620 (Zegocractin) at the time of demyelination in wild-type mice. At 7 dpl, 50 μM CM4620 treatment induced a significant increase in the proportion of mature $CC1^+$ OLs (Tukey $p = 0.017$). Thus, SOCE inhibitor treatment may act in a similar manner to *Stim1* cKO to promote differentiation. Future studies will determine the effects of *Stim1* cKO on remyelination, investigate the mechanisms of action of CM4620, and determine whether systemic treatment can influence remyelination in other models of demyelination. These results indicate that OPC-expressed Ca^{2+} sensing proteins can modulate OL differentiation following demyelination and may offer a novel therapeutic means to enhance myelin repair.

Disclosures: R. Ravichandar: None. **R. Muthaiah:** None. **D. Saraswat:** None. **F. Gadelkarim:** None. **R.A. Seidman:** None. **F.J. Sim:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.12/D22

Topic: B.10. Demyelinating Disorders

Support: NIH NINDS R01NS104021
DoD CDMRP MS220005

Title: 2-o sulfation of OPC-expressed heparan sulfate impairs oligodendrocyte differentiation following experimental demyelination

Authors: *R. MUTHAIAH[1], R. RAVICHANDAR[1], B. KULKARNI[1], R. JUSZCZAK[1], D. XU[2], F. J. SIM[1];
[1]Pharmacol. and Toxicology, [2]Oral Biol., The New York State Univ. at Buffalo, Buffalo, NY

Abstract: Chronic demyelination in multiple sclerosis (MS) is the result of a failed regenerative process known as remyelination. Remyelination largely occurs via the recruitment and differentiation of parenchymal oligodendrocyte progenitor cells (OPC). Deposition and alterations in the extracellular matrix following demyelination play a significant role in the failure of remyelination in MS and directly influences OPC signaling. We recently described a novel role of heparan sulfate proteoglycans (HSPGs) following experimental demyelination. 6-*O*-endosulfatases (*Sulf1/2*) specifically edit the pattern of 6-*O* sulfation (6S) on HSPGs post-synthetically and are highly expressed by human and mouse OPCs following demyelination. We have previously shown that the conditional knockout (cKO) of *Sulf-1/2* in OPCs accelerated recruitment, differentiation and remyelination following demyelination likely via inhibition of BMP and WNT signaling. In this study, we tested the hypothesis that the synthesis and pattern on sulfation on OPC-expressed HSPGs themselves plays a critical role in OPC function following demyelination and that removal of 2-*O* sulfation (2S) would result in altered OPC recruitment and/or differentiation. Adult *NG2creER;Hs2st1* floxed and cre-negative littermate controls were injected with tamoxifen prior to lysolecithin-induced spinal cord demyelination. Immunofluorescence for highly 2S/6S sulfated HSPG was enriched around a subset of OPCs at 7 days post lesion (dpl) and this was significantly reduced following *Hs2st1* cKO ($p = 0.01$). At 5 dpl, *Hs2st1* cKO did not alter OPC proliferation (%EdU$^+$) but was associated with a small increase in overall Olig2$^+$ oligodendrocyte (OL) lineage cell density. By 7 dpl, when OL differentiation occurs in this model, *Hs2st1* cKO significantly increased both OL lineage density and the proportion of CC1$^+$ mature oligodendrocyte among Olig2$^+$ cells ($p < 0.05$, $n = 5$ / group). Overall, this resulted in a more than 2-fold increase in oligodendrocyte density in *Hs2st1* cKO mice ($p < 0.01$). Ongoing studies will determine whether increased oligodendrogenesis following *Hs2st1* ablation is a direct result of loss of 2S or via a compensatory increase in 6S that is associated with improved remyelination. Together, these studies further implicate the role of HSPG dependent signaling in the context of demyelination and highlight the potential for HS modulators to enhance myelin repair.

Disclosures: R. Muthaiah: None. **R. Ravichandar:** None. **B. Kulkarni:** None. **R. Juszczak:** None. **D. Xu:** None. **F.J. Sim:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.13/D23

Topic: B.10. Demyelinating Disorders

Support: NIH Grant F31 AI174782

Title: Interleukin-12 Mediates OPC Maturation and Myelin Morphogenesis

Authors: A. MERCHAK, ***S. MOY**, A. THAKUR, L. BROWN, T. RAGHAVAN, R. BEITER, E. SLOGAR, A. GAULTIER;
Univ. of Virginia Neurosci. Program, Charlottesville, VA

Abstract: Multiple sclerosis (MS) is a multifaceted, chronic disorder of the central nervous system in which the myelin sheath is destroyed due to an autoimmune response. Despite decades of work, MS has no cure and remains a debilitating disease with an enormous economic and social cost. Research around remyelination and myelin maintenance during disease is ongoing. Harnessing the intrinsic signaling of oligolineage cells to promote maturation and differentiation of oligodendrocyte precursor cells (OPCs) into myelinating oligodendrocytes is one strategy for therapeutic intervention. Interleukin 12 (IL12) is a cytokine produced by macrophages, dendritic cells, and neutrophils in the periphery, and by microglia in the brain to promote T cell differentiation. We aimed to test the effects of IL-12 cytokine signaling in oligolineage cells during pathological demyelination such as that seen in MS. We incubated primary OPCs with IL-12 family cytokine which showed a reduction of relative expression of *Myrf* and *Mbp*, transcripts involved in myelin formation. Primary cultures from IL12Rβ2-/- mice do not differentiate compared to cultures from C57BI/6J mice. We used immunofluorescent imaging to visualize the organization of OPCs and oligodendrocytes within the corpus callosum. Female IL12Rβ2-/- mice have disrupted myelin formation including disorganized axonal tracts and higher counts of OPCs, while male mice showed no differences between IL12Rβ2-/- and their C57BI/6J age-matched counterparts (10-15 weeks old). Taken together, these results suggest that the absence of IL12 shown in our constitutive IL12Rβ2 knockout has a detrimental effect on the maturation and differentiation of OPCs into myelinating oligodendrocytes both *in vitro* and *in vivo*. Conversely, data from the stimulation of cells with IL12 suggests that overproduction of IL12 may also have an inhibitory effect on OPC differentiation, highlighting the necessity of appropriate IL12 levels in the brain. These studies underscore the importance of understanding age-specific differences in neuroimmune signaling to find effective therapeutics for MS and other demyelinating disorders such as Alzheimer's disease.

Disclosures: A. Merchak: None. **S. Moy:** None. **A. Thakur:** None. **L. Brown:** None. **T. Raghavan:** None. **R. Beiter:** None. **E. Slogar:** None. **A. Gaultier:** None.

Poster

PSTR254. Oligodendrocytes and Myelin Function: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.14/D24

Topic: B.10. Demyelinating Disorders

Support: JSPS KAKENHI Grant JP19K16623
Kaeko Asada research donation

Title: Voltage-sensitive dye imaging reveals disrupted interhemispheric communication in a cuprizone-induced demyelination mouse model of multiple sclerosis

Authors: *K. TSUKUDA[1,2], M. MIWA[3], M. TAKETOSHI[2], Y. TOMINAGA[2], K. NAKASHIMA[1,2,3], T. TOMINAGA[1,2,3];
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Abstract: Multiple sclerosis (MS) is a chronic neurological disease associated with extensive demyelination within the central nervous system (CNS). Although the cause of MS onset is unclear, animal models such as autoimmune encephalomyelitis (EAE) and cuprizone (CPZ)-fed mice induce demyelination and are used as MS pathology. The corpus callosum (CC) plays a critical role in facilitating interhemispheric communication between layer II/III neurons in the cerebral cortex and is frequently affected by demyelination in both animal models and human patients. Although previous studies have investigated the electrophysiological aspects of nerve conduction in models of demyelination within the CC, a comprehensive understanding of its impact on interhemispheric communication remains to be discovered. Therefore, the aim of this study was to investigate the effects of demyelination on interhemispheric communication across the CC by visualizing neural circuit activity using voltage-sensitive dye (VSD). The CPZ-induced model of MS (CPZ mice) was established by subjecting male C57BL/6 mice to a 0.3% CPZ-containing powdered diet for six weeks. Acute coronal brain slices of 350 μm thickness were used in the study, ranging from 1 to -0.5 mm from the bregma. We used a wide-field microscope with an imaging system (MiCAM05, Brainvision Ltd.) that is designed for a large field of view (10 mm). We used SR95331 (Gabazine: GZ; 10 μM), a GABAA receptor inhibitor, to enhance interhemispheric connectivity throughout the experiments. Upon electrical stimulation of cingulate cortex area 1 (Cg1) within the anterior cingulate cortex (ACC), a significant optical excitatory signal propagated across cortical layers toward Cg2 in both control and CPZ mice. In control mice, this propagation resulted in interhemispheric spread across the CC. However, the interhemispheric spread was rarely observed in slices obtained from CPZ mice. These results suggest that the transmission of neural excitation to the opposite side across the CC is reduced due to demyelination. The slices showing decreased interhemispheric connectivity in CPZ mice showed demyelination on histological analysis. These results suggest that demyelination induced by the CPZ mouse model disrupts efficient action potential propagation between the left and right cerebral cortices through the CC. By employing optical imaging techniques, we can gain valuable insights into the pathophysiology of MS and explore potential therapeutic approaches and novel treatments.

Disclosures: K. Tsukuda: None. **M. Miwa:** None. **M. Taketoshi:** None. **Y. Tominaga:** None. **K. Nakashima:** None. **T. Tominaga:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.01/D25

Topic: B.11. Neuro-Oncology

Support: NSF EFRI CEE 2129617

Title: Extracellular matrix rigidity stimulates multiple bioenergetic pathways of the glioblastoma cells

Authors: *C. PAYNE[1], P. VILLARREAL[3], M. SOWERS[3], S. H. BOSSMANN[4], M. MOTAMEDI[3], B. SZCZESNY[3], G. VARGAS[2];
[1]Univ. of Texas Med. Br., Galveston, TX; [2]Neurosci. Cell Biol. and Anat., Univ. of Texas Med. Br., League City, TX; [3]UTMB-Galveston, Galveston, TX; [4]Kansas State, Manhattan, KS

Abstract: Glioblastoma (GBM) is a highly aggressive and invasive form of brain cancer. The 5-year survival rate of those diagnosed with GBM is less than 10% and, on average, patients have 12-15 months of survival following final diagnosis. Recent research has implicated mechanobiology in the development of the aggressive phenotype of this cancer, in which biochemical and biophysical cues encoded in the tumor microenvironment may promote cell proliferation and invasion. The extracellular matrix (ECM) is a critical component of the microenvironment and stiffening of the GBM ECM has been shown to enhance GBM cell migration and proliferation. Metabolic reprogramming is likely needed to support this proliferative and migration response but the specific changes as they relate to microenvironmental stiffness are not yet known. The purpose of this study was to investigate the effect of ECM stiffness on the metabolic profile of GBM cells. To do this, we seeded U87MG cells on premanufactured collagen coated hydrogels of 100Pa, 4kPa, and 25kPa stiffness and conducted a variety of assays that included mass spectrometry based metabolomics, label-free two-photon imaging for optical REDOX ratio (NADH/FAD) providing spatial cellular assessment and heterogeneity and morphometry, RNA sequencing, and imaging of cell migration. Results were indicative of metabolic reprogramming stimulated by increased ECM stiffness, which was accompanied by changes in cell morphology and migration. Metabolomic data indicated an increase in key metabolites and amino acids along the aerobic glycolysis and glutamine metabolism pathways as ECM rigidity increased, suggesting that metabolic activity across multiple pathways is affected by ECM rigidity. Both metabolomics data and two-photon imaging of the optical REDOX ratio, identified a decrease in FAD and an increase of NADH as ECM stiffness increased. These results indicated a decrease in oxidative phosphorylation with an increase in ECM stiffness, suggesting ECM stiffening signals for transition from oxidative phosphorylation to glycolysis. RNA sequencing identified over 100 significant changes in RNA expression between both the 100 and 4kPa and the 100 and 25kPa stiffnesses, and provide insight into the effect ECM rigidity has on gene expression relating to metabolism and cell proliferation. This study shows that metabolic reprogramming occurs in U87MG cells toward

increased glycolysis and glutaminolysis as the ECM stiffness increases, indicating a potential link between the biomechanical microenvironment with metabolic activity that could support the aggressive and lethal nature of GBM.

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Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.02/D26

Topic: B.11. Neuro-Oncology

Support: GSBTM Grant IV63GO
LTMT JRS award

Title: Hypoxic glioblastoma-derived extracellular vesicles induce microglial polarization to pro-tumorigenic phenotype

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Abstract: Glioblastoma multiforme (GBM) is marked by its highly heterogeneous, immunosuppressive, and hypoxic tumor microenvironment (TME) often resulting into limited success in therapies against GBM. Brain resident immune cells microglia are reprogrammed to an immunosuppressive phenotype by GBM tumor cells via release of extracellular vesicles carrying oncogenic immunomodulatory non-coding molecules such as long noncoding RNAs (lncRNAs). Although many lncRNAs are dysregulated in GBM, much is still unknown regarding its involvement in microglial polarization and pathophysiology. Here, we investigated the involvement of hypoxic glioblastoma-derived extracellular vesicles (GDEVs) in microglial polarization to a pro-tumorigenic phenotype with the enriched expression of H19 lncRNA in glioblastoma-derived exosomes. Human GBM cells (U87MG) were subjected to normoxic and hypoxic stimulus to closely mimic the *in vivo* TME. Results demonstrated the increase in the number of hypoxic exosomes release ($9.8*10^7$ particles/ml) as compared to normoxic ($6.0*10^7$ particles/ml) when characterized through Zeta view (NTA). *In-silico* database search and lncRNA profiling for glioblastoma-derived exosomes identified the enrichment of lncRNA H19 in hypoxic exosomes that is widely known to aid in GBM proliferation. To further study the functional effect of hypoxic exosomes on recipient microglia, we demonstrated nuclear localization of purinergic receptor (P2RY12) in microglia when co-incubated with hypoxic U87MG exosomes. The results obtained are in line with the studies suggesting the association of nuclear localization of P2RY12 with the increase in glioma grade and microglial chemotaxis. Hypoxic conditioned media treatment to microglia for 24 hrs significantly increased the

expression of M2 activated genes CD163, CD206, IL-10, STAT-3, PPAR-γ, ADORA-3, TMEM-119 and reduced phagocytic index thereby suggesting the induction of M2 like phenotype and altered phagocytosis. Together, our findings provide evidence to the involvement of GDEVs in microglial activation which enables us to further study the substantial role of lncRNA H19 in microglial dysregulation and its potential as a key biomarker for GBM.

Disclosures: **S. Pancholi:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); LTMT. **P. Pillai:** 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.; GSBTM.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.03/D27

Topic: B.11. Neuro-Oncology

Title: Antiproliferative and apoptotic effects induced by Ibervillae sonorae root extract in glioma cell lines

Authors: *C. RODRÍGUEZ-PÉREZ[1], M. A. TORRES-RAMOS[2], C. TREJO-SOLÍS[2]; [1]Natl. Inst. of Neurol. and Neurosurg., MEXICO CITY, Mexico; [2]Inst. Nacional de Neurología y Neurocirugía, Mexico City, Mexico

Abstract: Bioactive compounds in medicinal plants may be a good source of new treatments for diseases like cancer. One of the most aggressive nervous system tumors is the glioblastoma multiforme, which, despite new drugs, is still mortal and has a low survival rate. This study aimed to characterize and know the antiproliferative effects of *Ibervillae sonorae* over human glioma cell lines. *Ibervillae sonorae* is a plant from the Northwest of Mexico used traditionally for natives to treat diabetes and dermis infections. Root extracts of *Ibervillae sonorae* were obtained, and their effects on cellular proliferation and apoptosis in LN18 and U87 glioblastoma cell lines were evaluated. The results showed a dose-response and time-dependent effect on cell viability using the MTT assay and the downregulation of PCNA and cyclin D3. Also, the apoptotic cell death by the TUNEL test and western blot for Bcl-2, Bax, and Caspase 3 proteins were observed. The extract doesn't show a cytotoxic effect on the fibroblast BJ cell line.

Disclosures: **C. Rodríguez-Pérez:** None. **M.A. Torres-Ramos:** None. **C. Trejo-Solís:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.04/D28

Topic: B.11. Neuro-Oncology

Support: TL1TR002016

Title: Extracellular vesicle characteristics in response to iron in glioblastoma cell types

Authors: *E. TUFANO[1], K. PALSA[2], J. CONNOR[2];
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Abstract: Glioblastoma (GBM) is a very aggressive brain tumor with poor survival rates, emphasizing the need to understand the molecular mechanisms behind the disease. Extracellular vesicles (EVs) play extensive roles in GBM progression, including cell migration, invasion, immune responses, and treatment resistance. Iron is a key element that promotes GBM cell proliferation and is preferentially taken up and used by cancer stem cells (CSCs) to promote their growth. However, little is known about how iron impacts GBM EV number, cargoes, and functionality. Iron has been shown to increase CD63 positive vesicle release in several cell types due to the presence of an iron responsive element (IRE) in the 5' untranslated region (UTR) of this protein. Here, we examine the influence of iron on EV release from two GBM cell lines, T387 and LN229, which are CSC and non-CSC lines, respectively. Using Nanoparticle tracking analysis (NTA), we have found that 100 μM of ferric ammonium citrate (FAC) increases EV release in the CSC line after 24 hours compared to the untreated control, but not the non-CSC line. These data are complemented by changes to CD63 expression by Western blot in the CSC line, reflective of the IRE. We further find that these differences in EV release are rescued upon treatment with an EV inhibitor (GW4869) in the CSC cell line, but not the non-CSCs, looking at total EVs by Western blotting. These results suggest key mechanistic differences in EV release in response to iron between these cell populations in the tumor microenvironment (TME), prompting our interest in the related EV cargoes. Differences in iron metabolism between CSC and non-CSCs in GBM have been extensively studied, but the discrepancy in EV characteristics between these cells is a novel concept. Iron has been shown to influence several miRNAs that target iron uptake and release proteins within the parent cell that may be present within the EVs, contributing to altered iron metabolism within the tumor. To understand these differences further, we will interrogate specific miRNA and mRNAs that may contribute to GBM progression through horizontal transfer of cargoes within the TME using RNA sequencing. Together, this project provides a significant contribution to our understanding of how GBM EVs seed new tumor growth in response to high iron conditions, the contribution of iron-induced CSC and non-CSC EVs, and the specific EV cargoes that can be targeted to prevent new growth.

Disclosures: E. Tufano: None. **K. Palsa:** None. **J. Connor:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.05/D29

Topic: B.11. Neuro-Oncology

Title: Involvements of decapping scavenger enzyme DcpS in the progression of glioblastoma

Authors: U. KUDO, Y. KUSE, S. NAKAMURA, *M. SHIMAZAWA;
Mol. Pharmacology, Dept. of Biofunctional Evaluation, Gifu Pharmaceut. Univ., Gifu, Japan

Abstract: Glioblastoma (GBM) is a brain tumor derived from astrocytes and is the most poor prognosis cancer type among brain tumors. For GBM, temozolomide, an oral alkylating agent, is used as a first-line treatment, but the 5-year survival rate is only about 10%. Therefore, there is a worldwide expectation to develop new drugs against GBM. In this situation, a new therapeutic target of interest is the regulation of alternative splicing of carcinogenicity. Thus, we focused on RG3039, an decapping scavenger enzyme (DcpS) inhibitor, which can penetrate the blood-brain barrier and be used orally. DcpS binds to the 5' capping structure of mRNA and is involved in mRNA decay. DcpS is also reported to be responsible for the organization of the mRNA splicing complex and is implicated in cell proliferation of acute myeloid leukemia. In this study, we investigated whether DcpS contributes to the progression of GBM.First, bioinformatics analysis using Gliovis, the public database, was used to examine DcpS expression and survival by DcpS expression levels in GBM patients. We further explored the function of DcpS using two GBM cell lines, U87 and GL261. After treatment of U87 and GL261 cells with RG3039, cell proliferation was examined using CCK-8 and BrdU. Also, the expression of cell cycle-related proteins in U87 cells treated with RG3039 was evaluated using Western blot analysis. Furthermore, we examined the effects of siRNA-induced knockdown of DcpS in U87 cells on cell viability and expression of related proteins.Analysis utilizing Gliobis showed that DcpS is highly expressed in GBM patients and that GBM patients with high DcpS expression have lower survival rates than those with low DcpS. The DcpS inhibitor RG3039 significantly reduced cell viability and cell proliferation in U87 and GL261 cells. On the other hand, RG3039 did not decrease cell viability in non-tumor (astrocyte) cells. These results suggest that DcsS plays a particularly important role in survival and proliferation in GBM cells. RG3039 also decreased the expression levels of CyclinB1 and CyclinD1. Furthermore, the knockdown of DcpS in U87 cells reduced cell viability. Interestingly, knocking down DcpS in U87 cells reduced the expression of N-cadherin. N-cadherin is one of the major intercellular adhesion molecules and is known to induce interactions such as proliferation and differentiation in various cancer cells. Taken together, these results suggested that DcpS contributes to GBM progression through the expression of N-cadherin, and DcpS selective inhibitors are expected to be a novel treatment for GBM.

Disclosures: U. Kudo: None. **Y. Kuse:** None. **S. Nakamura:** None. **M. Shimazawa:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.06/Web Only

Topic: B.11. Neuro-Oncology

Support: NRF-2021R1A2C1095168
NRF-2020M2D9A2092373

Title: The repetitive evolution of neural stem cells contributes to the recurrence of glioblastoma

Authors: *J. LEE, X. LI;
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Abstract: Glioblastoma multiforme (GBM) mostly recurs locally near the resection cavity, causing high lethality of GBM, while primary treatment has been intensified to eradicate the possible residual local tumors. Otherwise, Neural stem cells (NSCs) in the subventricular zone (SVZ) have recently been identified as the cells of origin for human GBM. We hypothesized that the tumor-initiating neural stem cells in the SVZ might evolve repetitively to tumor construction following the removal of primary tumor, leading to the recurrent GBM. To do so, we developed a mouse model harboring the cancer-driving mutations in the NSCs of the SVZ with surgical resection to reflect the brain status after surgical resection of primary tumors, as well as the origin thereof. Therein, the NSCs harboring driver mutations migrated specifically to the RC through the aberrant growth of oligodendrocyte-precursor cells (OPCs). The SVZ-originated cells arriving at the RC newly constituted the locally recurrent GBM around the RC, representing the main pattern of recurrence in GBM. RNA sequencing analysis of longitudinal sampling from the mouse model and the matched primary-recurrence samples of human GBM patients revealed upregulation of the C-X-C Motif chemokine receptor (CXCR) 4/C-X-C motif chemokine ligand (CXCL) 12 axis in recurrent tumors after total resection. The microglia/macrophage activated by the resection can release CXCL12 to drive the aberrant migration of CXCR4-expressing NSC in the subventricular zone. We found that a CXCR4 antagonist inhibited the differentiation to OPC lineages from NSCs and decreased the number of immigrating OPC lineages to the RC in mice. The CXCR4/CXCL12 blockade also reduced mouse tumor development and death rates after resection. Accordingly, this study identifies the noble process of recurrence which the tumor-initiating NSCs can evoke repetitive cyclic evolution to the recurrent GBM even after the complete removal of the tumor. Blocking the CXCL12/CXCR4 pathway could be a potential treatment target to prevent this recurrence.

Disclosures: **J. Lee:** None. **X. Li:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

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Program #/Poster #: PSTR255.07/D30

Topic: B.11. Neuro-Oncology

Support: The Jordan and Kyra Memorial Foundation (MCH)
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Title: Characterizing cholinergic signaling in glioma stem cells

Authors: S. V. ANAND[1], M. K. LEE[1], A. G. SKORPUT[1,2], ***I. B. FOX**[3], B. C. CHRISTENSEN[1,4], A. T. GULLEDGE[1], M. C. HAVRDA[1,4];
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Abstract: Primary gliomas make up the majority of malignant tumors arising in the central nervous system and are the deadliest form of brain cancer. The current standard of care is surgical resection followed by chemotherapy with temozolomide and radiotherapy. Unfortunately, the recurrence of drug-resistant tumors is common leaving glioblastoma patients with a 5% five-year survival rate. Glioma stem cells (GSCs) are a subset of undifferentiated cells widely believed to drive tumor initiation, therapeutic resistance, and glioma recurrence. Depleting the GSC population in combination with the standard of care could improve current cancer treatments and extend the survival of glioma patients. Oligodendrocyte precursor-like GSCs have been identified as a cellular origin for glioma. Recent findings indicate that the neurotransmitter acetylcholine (ACh) maintains the primitive state of normal oligodendrocyte precursors via muscarinic ACh receptors (mAChRs), preventing cell cycle exit and maturation. Our analysis of publicly available data identified high levels of expression of *CHRM3* (M3mAChR) in adult and pediatric gliomas. CHRM3 expression was largely restricted to the proneural subtype of glioma that is associated with the oligodendroglial precursor gene expression signature. Oligodendrocyte precursor-like GSCs established from malignant oligodendrogliomas arising in mice express *Chrm3* and are responsive to ACh. Pharmacological studies in vitro and in vivo indicated that the FDA-approved anti-muscarinic drug benztropine suppressed GSC proliferation and glioma progression in serially passaged patient-derived glioma xenografts. These studies suggest that the cholinergic microenvironment may influence GSC malignant potential providing a rationale to investigate widely available antimuscarinics as treatments for glioma.

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Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

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Program #/Poster #: PSTR255.08/D31

Topic: B.11. Neuro-Oncology

Support: NRF Grant 2019M3C1B8090842
TSA Grant 6-2022-0147

Title: Characterization of Store-operated calcium entry in glioblastoma cell of origin

Authors: *S. KIM[1], S. CHUNG[2];
[1]YONSEI UNIVERISTY, SEOUL, Korea, Republic of; [2]Yonsei Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Recent scientific advances have been made to unravel the presence of neural circuit between the cortical neurons and brain tumor cells such as glioblastoma. The anatomical niche of brain tumor cells surrounded by the cortical neurons allow a neural influence over the tumor microenvironment and vice versa. So far, little is known about the functional role of the calcium signaling as a switch in the proliferation and migration of glioblastoma cells of origin. In this study, we characterized the glioblastoma cells of origin from the murine models in attempting to investigate the molecular signaling pathway involved. Using calcium imaging study with Fura-2/AM, our results indicated that glioblastoma cells of origin exhibited the store-operated Ca^{2+} entry (SOCE) channels. We found that activating the SOCE by store-depletion caused the calcium influx from the external environment. The blockade with SOCE inhibitor, GSK7975A, showed a significant reduction of the calcium influx in the cells, indicating the engagement of SOCE channels. We conducted these experiments to understand a voltage-independent source of calcium and its regulation in glioblastoma cells of origin where calcium may be a critical messenger to initiate the tumor proliferation and migration. Taken together, our results showed that the SOCE channels regulate the Ca^{2+} signaling of glioblastoma cells of origin, implicating in tumor progression.

Disclosures: S. Kim: None. **S. Chung:** None.

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PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

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Topic: B.11. Neuro-Oncology

Support: Austrian Science Fund (FWF) P 28909

Title: Sprouty2 regulates endocytosis and degradation of fibroblast growth factor receptor 1 in glioblastoma cells

Authors: *B. HAUSOTT[1], L. PIRCHER[1], M. KIND[1], J.-W. PARK[2], P. CLAUS[3], L. KLIMASCHEWSKI[1];
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Abstract: Endocytic trafficking of receptor tyrosine kinases (RTKs) regulates spatio-temporal intracellular signaling, and aberrant RTK signaling is a common phenomenon observed in glioblastoma (GBM). The Sprouty (SPRY) proteins are evolutionary conserved modulators of RTK signaling. SPRY2 inhibits fibroblast growth factor (FGF) signaling, whereas it enhances epidermal growth factor (EGF) signaling through inhibition of EGF receptor (EGFR) ubiquitination, degradation and endocytosis. In this study, we analyzed the effects of SPRY2 on degradation and signaling of FGF receptor 1 (FGFR1) compared to EGFR using two human GBM cell lines with different endogenous SPRY2 levels. In U251 cells with low endogenous SPRY2 levels, SPRY2 was overexpressed, while in SF126 cells with high endogenous SPRY2 content, SPRY2 was downregulated using short hairpin (sh)RNA. FGFR1 ubiquitination and degradation were analyzed by immunoprecipitation and Western blotting. Transfection with FGFR1-enhanced green fluorescent protein (FGFR1-EGFP) and treatment with Cy3-labeled FGF2 (FGF2-Cy3) was used to study the effects of SPRY2 on FGFR1 endocytosis by confocal microscopy of whole cell images. Western blot analysis was performed to analyze the effects of SPRY2 on FGF2- and EGF-induced signaling. SPRY2 increased EGFR levels but reduced FGFR1 levels by enhanced c-casitas b-lineage lymphoma (c-CBL)-mediated ubiquitination and decreased N-cadherin protein. Furthermore, SPRY2 was present in anti-FGFR1 immunoprecipitates. SPRY2 inhibited clathrin- and caveolae-mediated endocytosis of FGFR1 and uptake of transferrin. FGF2-induced activation of extracellular signal-regulated kinase (ERK) and phospholipase Cγ1 (PLCγ1) was inhibited by SPRY2 whereas EGF-induced ERK and PLCγ1 phosphorylation was enhanced. Together, these results demonstrate a novel role of SPRY2 in degradation and endocytosis of FGFR1. SPRY2 enhanced c-CBL-mediated ubiquitination and degradation of FGFR1 and reduced N-cadherin, which inhibits FGFR1 ubiquitination and lysosomal degradation. Since SPRY2 inhibited FGF2-induced signaling and reduced FGFR1 protein, the inhibitory effect of SPRY2 on FGF signaling may at least in part be due to the enhanced degradation of FGFR1.

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PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

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Program #/Poster #: PSTR255.10/D33

Topic: B.11. Neuro-Oncology

Support: NIH (NCI) Grant 5K22CA258953

Title: Examining the role of BDNF-TrkB.T1 signaling on the brain tumor microenvironment

Authors: *L. MERINO GALAN[1], S. ORTIZ-ESPINOSA[2], M. HATHAWAY[1], A. RAJENDRAN[1,3], G. RUBIO[1], M. SHABAR[3], N. RECHE-LEY[1], H. L. JAGANA[1], S. S. PATTWELL[1,2,3];

[1]Ben Towne Ctr. for Childhood Cancer Res., Seattle Children's Res. Inst., Seattle, WA; [2]Human Biol. Div., Fred Hutchinson Cancer Ctr., Seattle, WA; [3]Univ. of Washingthon, Seattle, WA

Abstract: Gliomas are the most common type of brain tumor in both children and adults. Communication between cancer cells and surrounding non-cancerous cells is a fundamental component of brain cancer pathophysiology. Glioma cells release factors that function as chemoattractants and influence the tumor microenvironment. Reciprocally, the activity of normal cells from the surrounding tumor microenvironment drives the proliferation and growth of glial malignancies through paracrine signaling, brain-derived neurotrophic factor (BDNF) being one of the key secreted factors. BDNF binds with high affinity to the tropomyosin receptor kinase B (TrkB). Recent work from our group has shown that the TrkB.T1 splice variant is upregulated in various human gliomas and that overexpressing TrkB.T1 enhances the tumor aggressiveness *in vivo* and is associated with the downregulation of genes involved in facilitating tumor cell recognition and elimination *in vitro.* However, the role of TrkB.T1 splice variant in this bidirectional communication between glioma cells and the surrounding cells remains unknown. Our aim was to assess if increased levels of TrkB.T1 observed in gliomas harbor a role in modulating immune responses. To explore these mechanisms *in vitro*, 3T3 cells were transduced with pLJM1-lentivirus to overexpress TrkB.T1 and then serum-starved and treated with BDNF. Immunoprecipitation and affinity purification-mass spectrometry (AP-MS) were used to identify TrkB.T1 interactors, and the conditioned media was subjected to a cytokine multiplex analysis. The results show that TrkB.T1 significantly increases key chemokine levels and that it has a unique set of binding partners involved in MHC class II-mediated immune response. In addition, we explored the immune cell heterogeneity associated with increased levels of TrkB.T1 *in vivo* using a glioma mouse model engineered with RCAS/tv-a technology. Taken together, this work shows that the BDNF-TrkB.T1 axis represents a potential target for modulating glioma-immune cell interactions needed to curb disease progression and warrants further investigation.

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Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

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Program #/Poster #: PSTR255.11/D34

Topic: B.11. Neuro-Oncology

Support: 5K22CA258953

Title: Elucidating the role of the TrkB.T1-initiated Ca^{2+} mobilization in Rho GTPase activation

Authors: *S. PATTWELL[1], **H. L. JAGANA**[2], M. HATHAWAY[2], A. RAJENDRAN[3], G. RUBIO[2], N. RECHE-LEY[4], M. SHABAR[5], L. MERINO GALAN[2], D. JOHNSON[2];

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Abstract: The neurotrophin receptor TrkB, along with its ligand brain derived neurotrophic factor (BDNF) are critical for proper neural development. The TrkB.T1 splice variant has been shown to be involved in glial development and is overexpressed across several cancers including low grade glioma and glioblastoma. TrkB.T1 stimulation by BDNF initiates a signaling cascade that has been shown to increase intracellular calcium in astrocytes. In addition, TrkB.T1 associates with Rho-GDI1 leading to morphological changes in astrocytes and glioma cells. Both calcium transients and Rho GTPases regulate oncogenic phenotypes including invasion and migration. Although links between TrkB.T1 and calcium signaling and TrkB.T1 with Rho GTPase activity have been individually identified, a gap on how they interact to regulate oncogenic characteristics remains. We hypothesize that TrkB.T1 initiated calcium mobilization is uniquely altering Rho activation and thereby regulating oncogenic phenotypes. Affinity purification mass spectrometry was utilized to identify both direct and indirect interacting proteins of TrkB.T1, full length-TrkB (TrkB.FL), and a GFP control. Gene Ontology (GO) analysis of these TrkB.T1 binding proteins revealed statistically significant terms related to GTPase activity, GTP/GDP Binding, Ca^{2+} mobilization, and Ca^{2+} ion binding. Calcium detection assays and calcium indicators facilitated deciphering of mechanistic differences in TrkB.T1-initiated calcium mobilizations in glial cells and and cancer cell lines. An *in vitro* Rho GTPase activity assay determined how changes in Ca^{2+} mobilization affect Rho activity. Deciphering the direct signaling cascade between calcium and Rho GTPases may reveal potential therapeutic vulnerabilities of gliomas. Future investigation into how gliomas are utilizing TrkB.T1 is needed to verify its promotion of oncogenic phenotypes.

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Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

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NIAAA T32 ARTN to BLM

Title: Glioblastoma initiation, migration, and cell types are regulated by core bHLH transcription factors ASCL1 and OLIG2

Authors: B. L. MYERS[1], L. E. PAEZ-BELTRAN[1], K. BRAYER[2], M. S. KEITH[1], J. NEWVILLE[1], C. K. MERTZ[1], R. ANDERSON[1], Y. LO[1], ***T. Y. VUE**[1];
[1]Neurosciences, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [2]Univ. of New Mexico Comprehensive Cancer Ctr., Albuquerque, NM

Abstract: ASCL1 and OLIG2 are basic-helix-loop-helix transcription factors (bHLH TFs) that are co-expressed in the majority of gliomas, including glioblastomas (GBMs), the most aggressive and heterogenous primary brain tumors. During development, these bHLH TFs bind to DNA E-box motifs to regulate transcriptional programs essential for neuronal and glial cell fate specification, migration, and proliferation, but their combinatorial roles in the development and heterogeneity of GBMs remains to be determined. In this study, we performed ChIP-seq and RNA-seq analyses of human GBMs to identify binding profiles and novel targets of both ASCL1 and OLIG2. We uncovered that ASCL1 and OLIG2 reciprocally interacts at the transcriptional and protein levels, and exhibit significant overlap in binding to transcriptional targets essential for GBM progression. Using loss and gain-of-function approaches, we then directly tested the combinatorial roles of ASCL1 and OLIG2 in brain tumors induced from glial progenitors in the dorsal cortex of a CRISPR/Cas 9 immunocompetent GBM mouse model. We showed that the loss of either *Ascl1* or *Olig2* significantly extended survival but also produced opposing tumor types, with ASCL1 promoting a highly invasive "astrocytoma" tumor type which consistently migrates across the corpus callosum, whereas OLIG2 represses this phenotype in favor of a less invasive "oligodendroglioma" tumor type. Despite these opposing functions, the loss of both *Ascl1* and *Olig2* drastically reduced the efficiency of tumor inductions, with 80% of mice failing to develop brain tumors by six months of age. This highlights the importance yet redundant function of these two bHLH TFs in the initiation of GBMs. Finally, using single cell RNA sequencing, we revealed that GBMs of the mouse model are transcriptionally diverse exhibiting molecular signatures of multiple GBM subtypes and cell types ranging from oligodendrocyte precursor cells to mature oligodendrocytes (OPC/MOL), neural stem cells to astrocytes (NSC/AS), and neurons to microglia. More importantly, tumor cells with high levels of ASCL1 are highly migratory, proliferative, and displayed molecular signatures resembling that of NSC/AS, consistent with ASCL1's role as a marker and regulator of glioma stem-like cells (GSCs). Taken together, this study demonstrates that oncogenic driver mutations lead to dysregulation of ASCL1 and OLIG2, which are then responsible for driving GBM initiation and progression in vivo. Subsequently, the dynamic level, interactions, and direct binding of these two bHLH TFs to each other and downstream target genes then determine the cell types and degree of migration of GBMs in the brain.

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Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

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Program #/Poster #: PSTR255.13/D37

Topic: B.11. Neuro-Oncology

Title: Distinct cell type profiles in healthy and glioblastoma human brain cortex samples using 10x Genomics Xenium in situ technology

Authors: *J. SICHERMAN, A. KIM, A. KALAIMANI, B. NGUYEN, C. BERRIDGE, F. WAGNER, H. CHIRRA, K. BELHOCINE, M. OLIVEIRA, R. GANTT, S. TAYLOR, S. MOHABBAT;
10x Genomics, San Francisco, CA

Abstract: Glioblastoma is an aggressive form of brain cancer with a very poor prognosis for survival. Understanding the molecular and cellular changes that occur in glioblastoma is crucial for developing effective treatments and understanding disease progression. In this study, we applied 10x Genomics Xenium In Situ technology with the Human Brain Panel to profile gene expression in postmortem healthy and glioblastoma brain cortex samples.
We used a maximum likelihood classifier and performed unsupervised clustering with differential gene expression analysis to identify putative cell types and states. This approach allowed us to map gene expression patterns with high resolution and distinguish between different cell types within and between samples. Our results revealed distinct molecular signatures associated with different cell types in healthy and glioblastoma samples, providing new insights into the cellular changes that occur in this devastating disease. These findings highlight the potential of spatial transcriptomics for advancing our understanding of complex neurological disorders and for identifying new targets for therapeutic intervention.

Disclosures: J. Sicherman: A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **A. Kim:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **A. Kalaimani:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **B. Nguyen:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **C. Berridge:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **F. Wagner:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **H. Chirra:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **K. Belhocine:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **M. Oliveira:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **R. Gantt:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **S. Taylor:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc. **S. Mohabbat:** A. Employment/Salary (full or part-time):; 10x Genomics, Inc..

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.14/Web Only

Topic: B.11. Neuro-Oncology

Support: CONACyT Grant A1-S-40569
CONACyT Grant 419514

Title: Synergistic cytotoxic effect of the combination of melatonin with albendazole or albendazole sulfoxide on glioma cells through autophagy and apoptosis

Authors: *M. CERÓN[1,2], V. CHAVARRIA[4], C. RIOS[3], B. PINEDA[5], F. PALOMARES[6], I. ROJAS-TOMÉ[6], H. JUNG[7];
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Abstract: Introduction. Glioblastoma (GB) is the most aggressive and lethal brain tumor in adults, which presents diffuse cerebral infiltration, drug resistance and high recurrence. Currently, standard treatment involves maximal surgical resection, followed by radiation therapy and concurrent chemotherapy with temozolomide; however, the median overall survival is 12-15 months. New treatments (bevacizumab) have been approved for recurrent patients, but the average survival rate is two years. Therefore, it is necessary to continue exploring therapeutic alternatives that offer better results. Taking into account that the anticancer activity of albendazole (ALB), its active metabolite, albendazole sulfoxide (ALBSO) and melatonin (MLT), has been previously reported in various types of cells, through different mechanisms of action, the main objective of this study was to assess whether the combinations of MLT with ALB or MLT with ALBSO have a synergistic cytotoxic effect on glioma cells. Methods. C6 and RG2 rat glioma cells and U87 human glioma cells were used. Concentration-response curves were prepared in the range of 0.16 to 1.25 μM for ALB, 2.0 to 64.0 μM for ALBSO, and 0.18 to 6.0 mM for MLT. The mean Dose (Dm) values were calculated from which combinations were designed in serial dilutions. Cytotoxicity was evaluated using the MTT assay and drug interaction was determined by the Chou-Talalay method. The mechanisms of cell death, apoptosis, necrosis, (annexin V and 7-AAD) and autophagy (LC3 and AVOS), were evaluated by flow cytometry and immunofluorescence. The cell proliferation was evaluated by crystal violet staining. Results. Our results showed that in all cell lines the drugs exhibited cytotoxic activity in a concentration-dependent manner. The Dm values in lines C6, RG2 and U87, for ALB were 0.6 μM, 0.6 μM and 0.9 μM; for ALBSO, 20.0 μM, 26.0 μM and 36.0 μM; and for MLT, 1.0 mM, 0.9 mM, and 0.9 mM, respectively. Most of the combinations produced a synergistic cytotoxic effect. The combined treatments induced death in all three cell lines, mainly by apoptosis and autophagy. Inhibition of cell proliferation was observed after ALB and ALBSO treatment, as well as with the combination of both compounds with MLT. Conclusions. The synergistic cytotoxic effect of the combination of ALB and ALBSO with MLT could be related to the different mechanisms of action of the molecules. The results are promising since the combinations could be a potential strategy for the treatment of GB, considering that these compounds are less toxic and expensive. Other studies are necessary to evaluate the combinations in in vivo models.

Disclosures: **M. Cerón:** None. **V. Chavarria:** None. **C. Rios:** None. **B. Pineda:** None. **F. Palomares:** None. **I. Rojas-Tomé:** None. **H. Jung:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.15/D38

Topic: B.11. Neuro-Oncology

Support: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project number 326998133 – TRR 225 (subprojects C05/C02/Z02)

Title: Glioblastoma multiforme cells generate functional cell-cell interactions with native CNS cells in 3D in vitro ultra-soft hydrogels

Authors: M. S. ANDRADE MIER[1], J. SCHENK[3], K. G. HEINZE[3], T. BLUNK[2], *C. VILLMANN[1];
[1]Inst. for Clin. Neurobio., [2]Dept. of Trauma, Hand, Plastic and Reconstructive Surgery, Univ. Hosp. of Wuerzburg, Wuerzburg, Germany; [3]Rudolf Virchow Center, Ctr. for Integrative and Translational Bioimaging, Julius-Maximilians-University Wuerzburg, Wuerzburg, Germany

Abstract: Glioblastoma multiforme (GBM) are the most aggressive brain tumors. Despite the use of standard therapeutic approaches (surgery, chemotherapy, and radiotherapy), patients life expectancy is around 16 months after diagnosis due to GBM´s highly proliferative, infiltrative, and invasive properties. Recently, the interactions of glioma cells with neurons and astrocytes have been brought to the spotlight. Functional pseudo-synaptic cell-cell interactions between glioma cells and native central nervous system cells underlie tumor pathophysiology including invasion, tumor proliferation, and maintenance of an immunosuppressed environment. To further study these mechanisms, disease models that recapitulate the development of GBM are needed. A 3D *in vitro* hydrogel-based culture system was used to establish a model of glioblastoma with a controllable microenvironment. We used a hyaluronic acid-based hydrogel with very low stiffness (≈ 100 Pa) to mimic the mechanical properties and the chemical composition of the brain as hyaluronic acid is one of the major components in the brain extracellular matrix. Previously, it was demonstrated that co-cultures of cortical neurons and astrocytes were able to mature and formed a functional neuronal network. To stay within the murine system, tri-cultures of Gl-261, a mouse glioma cell line, together with primary cortical astrocytes and neurons were established to study functional cell-cell interactions. Immunocytochemical stainings revealed cell-cell contacts between glioma cells and astrocytes (gap-junctions) and neurons and glioma cells (microtubes). If these contact points represent functional interactions is currently under investigation. Confocal live-cell imaging of 3D tri-cultures will be used to track the movement of glioma cells and microtube formation, similarly a functional assessment of gap-junctions can be performed. Finally, calcium imaging will be used to determine if glioma cells integrate into the neuronal network and alter network firing. Altogether, the generated 3D *in vitro* constructs

mimic a “physiological” GBM microenvironment which allow glioma cells to develop functional cell interactions as reported for *in vivo* models. Such models are essential prerequisites to further generate patient-specific approaches to study and understand the disease pathomechanisms.

Disclosures: M.S. Andrade Mier: None. **J. Schenk:** None. **K.G. Heinze:** None. **T. Blunk:** None. **C. Villmann:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.16/D39

Topic: B.11. Neuro-Oncology

Support: German Research Foundation (Grant: FOR 2715)
Innovation under the Framework Partnership Agreement No. 650003 (HBP FPA)

Title: In vitro investigation of glioma-induced neuronal hyperexcitation using a human neuronal-glioblastoma co-culture model

Authors: *D. YANG[1], A. BAK[2], K. SCHMIED[2], H. KOCH[2], D. FELDMEYER[1], D. DELEV[3]; [1]Inst. of Neurosci. and Med. 10, Res. Ctr. Juelich, Juelich, Germany; [2]Dept of Neurology, Section Epileptology, [3]Dept of Neurosurg., RWTH Aachen Univ. Hosp., Aachen, Germany

Abstract: Glioblastoma is one of the most common and devastating malignant brain tumors, with an extremely poor prognosis, which is reflected in an overall survival of only 15 months despite maximal treatment. Glioma progression can lead to increased neuronal activity, resulting in neuronal hyperexcitability and the development of tumor-induced epilepsy. This clinical complication occurs in 40-80% of glioma patients. To study how glioma growth progressively alters neuron excitability, we transplanted ZsGreen-tagged brain tumor cells into human organotypic brain slice cultures obtained from cortical resection surgeries. We tagged endogenous neurons by introducing mCherry to neurons using Adeno-associated viruses (AAV) transduction. After 2 to 8 days in vitro (DIV), we performed whole-cell patch-clamp recordings from cortical layer 5 pyramidal neurons in tumoral, peritumoral, and non-tumoral areas. Our findings revealed that glioma invasion quickly affected neuronal excitability from the early days of transplantation. Neurons in tumoral and peritumoral areas showed a larger input resistance, broader AP half-width, and smaller rheobase current compared to neurons located in tumor-free area. Additionally, neurons located within the area of the tumor showed a markedly high frequency of excitatory post-synaptic currents (EPSCs). Thus, we successfully established a co-culture model to investigate the effects of glioma on the peritumoral neuronal microenvironment in the human cortex. This model will aid our understanding of how these brain tumor cells can integrate into complex neuronal circuits.

Disclosures: **D. Yang:** A. Employment/Salary (full or part-time):; Research Centre Juelich, RWTH Aachen University Hospital. **A. Bak:** None. **K. Schmied:** None. **H. Koch:** None. **D. Feldmeyer:** None. **D. Delev:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.17/D40

Topic: B.11. Neuro-Oncology

Support: The Sontag Foundation
NIH R01 NS123562

Title: Examining cellular vulnerabilities of glioblastoma across space and time using region-specific human brain organoids

Authors: ***T. N. BHATIA**[1], S. GANTA[1], S. SZABO[5], A. SING[1], A. KING[1], C. SOJKA[1], K. HOANG[2], E. NDUOM[2], T. GARZON-MUVDI[2], R. READ[3], J. OLSON[4], S. A. SLOAN[1]; [1]Dept. of Human Genet., [2]Dept. of Neurosurg., [3]Dept. of Pharmacol. and Chem. Biol., [4]Departments of Hematology, Med. Oncology, and Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA; [5]Georgia Inst. of Technol., Atlanta, GA

Abstract: Glioblastoma multiforme (GBM) is a devastating form of astrocytoma with no known cure. However, these tumors show significant regional bias. For example, most adult GBMs are localized to the frontotemporal lobes of the cerebral cortex. In contrast, adult GBMs are rarer in caudal regions, accounting for only ~1-5% of all cases in the midbrain and hindbrain. Thus, signals from the local environment may influence the biological behavior of GBM cells. However, the mechanisms underlying these phenomena have been difficult to study due to lack of access to functional human brain tissue. To address this question, we use region-specific human induced pluripotent stem cell-derived (hiPSC) brain organoids engrafted with cells harvested directly from surgical GBM resections or with patient-derived glioma stem cells (GSCs). Using RNA-seq and immunostaining we confirmed that forebrain, midbrain, and hindbrain organoids express canonical patterning markers. We dissociated surgical GBM resections and single-cell RNA sequencing confirmed cell type heterogeneity after dissociation. Specifically, immune cells as well as all major CNS cell types, such as microglia, oligodendroglia, astroglia, neurons, and radial glia were observed in dissociated GBMs. We show that dissociated surgical GBM cells and GSCs readily invade organoids patterned to mimic the dorsal cortex (pallium; hCS), ventral cortex (subpallium; hSS), midbrain (hMbS), and hindbrain/spinal cord (hSpS). However, GSCs tended to show a regional preference and occupied greater areas of forebrain *vs.* midbrain/hindbrain organoids. Finally, we report that tumor cells maintain their phenotype within organoids and express markers related to proliferation (Ki67, EdU), stemness (Sox2, Nestin, CD44), and glial precursors (GFAP, PTPRZ1). Currently, we are using single-cell approaches to determine how the host region

microenvironment influences the identity of GBM cells by comparing pre- and post-engraftment transcriptomes. Our findings will help identify novel targets to determine if endogenous defenses preexisting in select regional environments can be harnessed to stave off tumor formation, reduce relapse, or improve patient survival.

Disclosures: **T.N. Bhatia:** None. **S. Ganta:** None. **S. Szabo:** None. **A. Sing:** None. **A. King:** None. **C. Sojka:** None. **K. Hoang:** None. **E. Nduom:** None. **T. Garzon-Muvdi:** None. **R. Read:** None. **J. Olson:** None. **S.A. Sloan:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.18/D41

Topic: B.11. Neuro-Oncology

Support: Sontag Foundation
NIH R01 NS123562

Title: Engraftment of Patient Derived Glioblastoma Cell Lines into Brain Region Specific Organoids

Authors: *S. GANTA[1,2], T. N. BHATIA[2], A. KING[2], A. SING[2], R. REED[3], S. A. SLOAN[2]; [1]Emory Univ. Neurosci. and Behavioral Biol., Atlanta, GA; [2]Human Genet., [3]Pharmacol. and Chem. Biol., Emory Univ., Atlanta, GA

Abstract: Glioblastoma (GBM) is the most common malignant brain tumor in adults. GBMs are known for their highly invasive and proliferative properties and are associated with a dismal prognosis (~12-18 months post-diagnosis). Furthermore, these tumors show regional disparities, and the most frequent location for GBMs in adults is the cerebral cortex. In contrast, less than 5% of adult GBMs occur in the cerebellum, brainstem, and spinal cord. The mechanistic underpinnings of the observed regional differences in occurrence remain unclear but may be driven by regional differences in the cellular and molecular profiles of the brain microenvironment. This idea has been difficult to study due to a lack of human-specific models that effectively recapitulate the pathophysiology and biological behaviors of GBMs in region-specific microenvironments. To address these challenges, we employed a patient derived xenograft (PDX) model by engrafting GFP-tagged patient-derived glioma stem cells (GSCs) from three individuals into human induced pluripotent stem cell (hiPSC)-derived cortical and spinal cord organoids. Immunostaining assays were performed at 2, 7, 14, and 21-days post-engraftment to compare the extent of infiltration and proliferation within both the regions. Inter-regional differences were observed specific to each patient engraftment. We are currently determining the proliferative capacities of GSCs within cortical versus spinal cord organoid environments by measuring the co-expression of GFP with proliferative marker Ki67 and 5-Ethynyl-2′-deoxyuridine (EdU). In addition, we tended to observe that GSCs displayed

morphological complexity after entering the organoid environment, potentially suggesting that GSCs differentiate in their post-engraftment setting. To define the cellular and transcriptomic effects of GSC engraftment within organoids, we are performing RNA-sequencing and immunostaining with canonical neuronal, glial, and oligodendroglial markers. By comparing the biological behaviors of GSCs in cortical versus spinal cord organoids, we aim to gain insights into whether GBM's affinity for particular brain regions is intrinsic (driven by genetic mutations) or extrinsic (driven by the regional microenvironment), thus advancing our understanding of this devastating disease.

Disclosures: **S. Ganta:** A. Employment/Salary (full or part-time):; Emory University Department of Human Genetics. **T.N. Bhatia:** A. Employment/Salary (full or part-time):; Emory University Department of Human Genetics. **A. King:** A. Employment/Salary (full or part-time):; Emory University Department of Human Genetics. **A. Sing:** A. Employment/Salary (full or part-time):; Emory University Department of Human Genetics. **R. Reed:** A. Employment/Salary (full or part-time):; Emory University Department of Pharmacology and Chemical Biology. **S.A. Sloan:** A. Employment/Salary (full or part-time):; Emory University Department of Human Genetics.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.19/D42

Topic: B.11. Neuro-Oncology

Title: Functional ultrasound imaging of mouse orthotopic glioma

Authors: A. SHATILLO, ***J. RYTKÖNEN**, T.-K. STENIUS, R. IMMONEN, A. SUHONEN, S. BÄCK;
Charles River Discovery Services, Kuopio, Finland

Abstract: Aberrant vasculature together with neovascularization are hallmark of glioblastoma. Understanding the vasculature of glioma can have a pivotal role in planning therapeutics approaches. The objective of this study was to investigate morphological, vasculature and blood flow changes induced by aggressive tumor growth, using in vivo imaging - magnetic resonance imaging (MRI) and functional ultrasound (fUS) imaging in a mouse model of orthotopic glioma. Human glioblastoma xenografts, U-87M cells 5 x 10^4, were implanted in female NMRI nude mice at the age of 8 weeks. Four weeks after implantation the mice we anesthetized with isoflurane and scanned with 11.7 T small animal MRI (Bruker) for tumor volumetry. Thereafter, the mice were imaged with Iconeus One imaging system (Iconeus, Paris, France) for structural information of brain vasculature and relative cerebral blood volume (rCBV) changes. High resolution vascular imaging was performed after intravenous injection of microbubble contrast agent (SonoVue, sulphur hexafluoride microbubbles).
Four weeks after implantation the average tumor size was 58.8 ± 27.6 mm^3 (mean ± SD, n=7).

Aberrant vasculature was visualized with structural fUS imaging as and the necrotic core of the tumor was observed. A reduced rCBF was observed in ipsilateral hemisphere on the relative power doppler signal timeseries as a lower amplitude and faster decay compared to contralateral side.
As a summary, in vivo fUS imaging is a noninvasive tool to visualize vascular changes induced by aggressive brain tumor growth which are not detectable with conventional imaging methods (CT, MRI, PET, SPECT) and can provide a novel readout for efficacy studies.

Disclosures: **A. Shatillo:** A. Employment/Salary (full or part-time):; Charles River Discovery Services Finland. **J. Rytkönen:** A. Employment/Salary (full or part-time):; Charles River Discovery Services Finland. **T. Stenius:** A. Employment/Salary (full or part-time):; Charles River Discovery Services Finland. **R. Immonen:** A. Employment/Salary (full or part-time):; Charles River Discovery Services Finland. **A. Suhonen:** A. Employment/Salary (full or part-time):; Charles River Discovery Services Finland. **S. Bäck:** A. Employment/Salary (full or part-time):; Charles River Discovery Services Finland.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.20/D43

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01MH101214
NIH Grant R01MH108924
NIH Grant R01NS104944
NIH Grant R01DA050374

Title: Area postrema neurons mediate interleukin-6 function in cancer-associated cachexia

Authors: *Q. SUN, D. VAN DE LISDONK, B. GEGENHUBER, M. WU, J. TOLLKUHN, B. LI;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Interleukin-6 (IL-6) has been long considered a key player in cancer-associated cachexia. It is believed that sustained elevation of IL-6 production during cancer progression causes brain dysfunctions, which ultimately result in cachexia. However, how peripheral IL-6 influences the brain remains poorly understood. Here we show that neurons in the area postrema (AP), a circumventricular structure in the hindbrain, mediate the function of IL-6 in cancer-associated cachexia in mice. We found that circulating IL-6 rapidly enters the AP and activate AP neurons. Peripheral tumor leads to neuronal hyperactivity in the AP, and causes potentiated excitatory synaptic transmission onto AP neurons. Neutralization of IL-6 in the brain of tumor-bearing mice reduces AP hyperactivity, prevents cachexia, and markedly prolongs lifespan. Furthermore, suppression of Il6ra specifically in AP neurons achieves similar effects. Our study

identifies a central mechanism underlying the function of peripheral IL-6, which may serve as a target for treating cancer-associated cachexia.

Disclosures: Q. Sun: None. **D. Van De Lisdonk:** None. **B. Gegenhuber:** None. **M. Wu:** None. **J. Tollkuhn:** None. **B. Li:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.21/D44

Topic: B.11. Neuro-Oncology

Title: The Development and Application of a High-Plex Antibody Panel for Spatial Phenotyping of Mouse Brain Tissues in Homeostatic and Diseased states

Authors: D. KLYMYSHYN[1], ***A. PRATAPA**[2], N. JHAVERI[1], L. SHERRY[3], M. MACFARLANE[3], N. MAMMADOVA[1];
[1]Akoya Biosci., Marlborough, MA; [2]Akoya Biosci., Durham, NC; [3]OracleBio Ltd., Glasgow, United Kingdom

Abstract: The Glioblastoma multiforme (GBM) tumor microenvironment is highly immunosuppressive, leading to poor clinical outcomes and median survival of less than 15 months. Preclinical syngeneic mouse models are indispensable for analyzing the underlying pathogenesis and immunobiology of GBM, identifying novel therapeutic targets, and evaluating the efficacy of potential therapeutic strategies. In this study, we utilize a spatial phenotyping application that permits comprehensive characterization of key proteins in the microenvironment of healthy and diseased brain tissues. The PhenoCycler-Fusion is a fast spatial biology solution that affords ultra-high parameter single cell spatial readouts. We used this solution for deep phenotyping of over 40 proteins, comprising immune cell lineages, glial cell activation states, as well as markers for tumor, vascular, and neuronal landscapes of the murine GBM models. Via whole-slide spatial phenotyping and single-cell analysis, we were able to isolate distinct microglial, neuronal, and systemic immune subtypes within the GBM tissue microenvironment. Our data provides a comprehensive account of diverse immune cell populations in murine GBM models and may guide informed choices to facilitate immunotherapies in the clinic. Our application has enormous potential to further our understanding of the brain microenvironment in GBM and other CNS related disorders such as Alzheimer's and Parkinson's disease.

Disclosures: D. Klymyshyn: A. Employment/Salary (full or part-time):; Akoya Biosciences. **A. Pratapa:** A. Employment/Salary (full or part-time):; Akoya Biosciences. **N. Jhaveri:** A. Employment/Salary (full or part-time):; Akoya Biosciences. **L. Sherry:** A. Employment/Salary (full or part-time):; OracleBio Ltd. **M. MacFarlane:** A. Employment/Salary (full or part-time):; OracleBio Ltd. **N. Mammadova:** A. Employment/Salary (full or part-time):; Akoya Biosciences.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.22/Web Only

Topic: B.11. Neuro-Oncology

Title: An unusual case of gliosarcoma/glioblastoma with rhabdoid changes in a 31 year-old-man.

Authors: *L. DODDOLI-OLIVARES[1], D. Z. ARELLANO[1], E. GARCIA-BOLL[1], A. A. ANGELES[2];
[1]Med. school, Anáhuac Querétaro, Querétaro, Mexico; [2]Hosp. Infantil de Oncología (HITO), Querétaro, Mexico

Abstract: Glioblastoma, a type of brain tumor, encompasses various histological variants, including the rare gliosarcoma, which is known for its highly aggressive nature and limited number of documented cases. In this report, we present the case of a 31- year- old man who initially manifested a single seizure episode. A month later, he experienced weakness in his left hand, resulting in frequent dropping of objects. Brain MRI unveiled a mass in the right hemisphere that extended across the midline and obstructed the ventricular system. To address this, the patient underwent parieto-temporal resection surgery. Gross specimen histology indicated the coexistence of classic glioblastoma, gliosarcoma and glioblastoma with rhabdoid changes. Considering the aggressive nature of the tumor, adjuvant radiotherapy was administered after the surgical procedure. Histopathological examination indicated a tumor composed of pleomorphic glial cells, fusiform cells, and cells displaying rhabdoid changes, accompanied by areas of necrosis and microvascular proliferation. The tumor exhibited high cellular density, frequent atypical mitosis, and geographic necrosis. Immunohistochemical analysis exhibits positive expression of glial fibrillary acidic protein (GFAP) in neoplastic cells, with focal positivity for isocitrate dehydrogenase (IDH). The Ki67 labeling index, which indicates proliferative activity, was determined to be 40% in the tumor cells. The integrated diagnosis encompassed a gliosarcoma/glioblastoma with rhabdoid changes, wherein the classical glioblastoma component accounted for 30% of the tumor. According to the World Health Organization (WHO) grading system, the tumor was classified as grade 4. Molecular analysis confirmed an IDH wild type status and provided data on hypoxia and reactive gliosis. The therapeutic plan involved initiating volumetric modulated arc therapy (VMAT) with a total dose of 60 Gray, which was well-tolerated by the patient. This case emphasizes the intricate clinical presentation, aggressive histopathological features, and the essential role of radiotherapy following surgery in managing refractory glioblastomas, particularly in young individuals.

Disclosures: L. Doddoli-Olivares: None. **D.Z. Arellano:** None. **E. Garcia-Boll:** None. **A.A. Angeles:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.23/D45

Topic: B.11. Neuro-Oncology

Title: Occult gallbladder adenocarcinoma with spinal leptomeningeal spread mimicking Guillain Barré syndrome. Post-mortem case report

Authors: *R. ORTEGA[1], J. E. GARCÍA-BOLL[1], A. A. ANGELES-ROMERO[1,2], K. LÓPEZ-MAGALLÓN[3], E. GÓMEZ-APO[3,4];
[1]Univ. Anáhuac Querétaro, Escuela de Medicina, Querétaro, Mexico; [2]Hosp. Infantil de Oncología (HITO), Querétaro, Mexico; [3]Hosp. Gen. de México, Dr. Eduardo Liceaga, Querétaro, Mexico; [4], Univ. Nacional Autónoma de México, Facultad de Medicina, Ciudad de México, Mexico

Abstract: Guillain-Barré syndrome (GBS) is an autoimmune disorder characterized by acute and subacute polyneuropathy with diverse clinical presentations. While peripheral involvement primarily affecting the myelin sheath is more common, axonal and retrograde involvement represent a less frequent yet aggressive variant. GBS is typically associated with concurrent bacterial and viral infections; however, rare cases demonstrate a cross-reactive response in patients with cancer; notably, lymphatic, hematopoietic, lung, prostate, mammary, and male genital tissues, along with the use of chemotherapeutic agents. Here, we present an unusual case of a 51-year-old woman with a history of obesity and tobacco use, who exhibited rapidly progressive motor axonal demyelinating polyradiculomyelopathy, resulting in ascending weakness, areflexia, quadriparesis, cranial nerve involvement, and dysautonomia. Symptoms did not improved even after plasmapheresis treatment. CT scan revealed diffuse cerebral and cerebellar edema. The patient continued with neurological impairment and died. Remarkably, histopathological examination during autopsy unveiled a moderately differentiated adenocarcinoma of the gallbladder with multi-organ metastases, including the liver, adrenal glands, and ovaries; as well as cervical, peripancreatic, periaortic, and perirenal lymph nodes; and in the central nervous system (basal ganglia, frontal lobe leptomeninges, and spinal cord leptomeninges). Notably, central chromatolysis was observed in the anterior horns of the spinal cord. This atypical case highlights the severe expression of Guillain-Barré syndrome as a paraneoplastic manifestation, particularly in a patient without a history of significant infections.

Disclosures: R. Ortega: None. **J.E. García-boll:** None. **A.A. Angeles-romero:** None. **K. López-magallón:** None. **E. Gómez-apo:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.24/D46

Topic: B.11. Neuro-Oncology

Title: Lateral proteome transfer between sensory neurons and breast cancer

Authors: *Y. WU, J. C. BORNIGER;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Recent evidence suggests a crucial involvement of the nervous system in the development of cancer. The bidirectional interaction between the nervous system and cancer occurs either through direct membrane contacts or tumor microenvironment. Compared to investigations on nerves-glioma interactions in the brain, studies exploring the role of the peripheral nervous system in the tumor microenvironment outside the brain are relatively limited.
Breast tumor clearing results indicate sensory nerves are the most abundant nerve types in the tumor microenvironment throughout the early to late stages during tumor progression. We have established a co-culture system where breast cancer cells are found in direct contact with primary sensory neurons. Interestingly, a significant increase of proliferation and migration rate of breast cancer cells were observed, particularly when stromal cells are present in the neuron cultures. Through bulk RNA-sequencing analysis, we have identified the upregulation of several key cell signaling pathways involved in cell adhesion, migration, and proliferation in the co-cultured breast cancer cells. Furthermore, using bioorthogonal labeling, proximity labeling enzymes and immunostaining, we demonstrated intercellular protein and mitochondria trafficking between sensory neurons and breast cancer cells. This lateral cellular component transfer may implicate in cellular homeostasis, damaged cell repair, tumor progression and immunoregulation.
To further elucidate the mechanisms underlying this sensory neuron-cancer cell interaction, our research focuses on identifying the specific proteins being trafficked, investigating the structural aspects of the cellular connections involved, and understanding their functional implications. This will be achieved through techniques such as mass spectrometry, electron microscopy, whole-cell patch-clamp recording, microelectrode array, and intravital imaging, etc.
By studying the interactions between the peripheral nervous system and breast cancer within the tumor microenvironment, we aim to gain a comprehensive understanding of the molecular and cellular mechanisms driving breast cancer progression and potentially identify novel therapeutic targets.

Disclosures: **Y. Wu:** A. Employment/Salary (full or part-time):; Cold Spring Harbor Laboratory. **J.C. Borniger:** A. Employment/Salary (full or part-time):; Cold Spring Harbor Laboratory.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.25/D47

Topic: B.11. Neuro-Oncology

Support: CIHR Grant #451168.

Title: Incidence of Intracranial Tumours in Aged Spontaneously Hypertensive Rats

Authors: *A. C. J. KALISVAART[1], F. K. H. VAN LANDEGHEM[4,2], C. WILKINSON[3], F. COLBOURNE[1,2];
[1]Psychology, [2]Neurosci. and Mental Hlth. Inst., [3]Res. Ethics Office, Univ. of Alberta, Edmonton, AB, Canada; [4]Lab. Med. and Pathology, Univ. of Alberta Hosp., Edmonton, AB, Canada

Abstract: Background: Worldwide, annual incidence of intracranial tumours is approximately 20 per 100,000 people, or ~1.6 million based on the current global population. The risk of developing a primary intracranial tumour increases with age. Modelling these cancers accurately using translationally relevant animal models remains a challenge. Therefore, tracking tumour incidence and pathophysiology in laboratory animal species and sub-strains as they age naturally remains a valuable exercise in understanding cancer etiology, and is also relevant to modelling other age-related pathologies; here, we document our observations in aged spontaneously hypertensive rats (SHRs), a laboratory rat strain frequently used in cardiovascular research. **Methods:** Sixty male SHRs were aged to 20-24 months for other experiments. Intracranial tumour incidence was documented upon post-mortem necropsy following either: a) spontaneous death in cage, b) displaying clinical signs (e.g., ataxia, loss of balance/coordination, visual deficits), meeting premature euthanasia criteria, or c) upon serendipitous observation following euthanasia (e.g., no obvious clinical signs). Tissue samples were taken for assessment in consult with a neuropathologist (H&E, immunohistochemistry, transmission electron microscopy). **Results:** In our sample, 18 out of 60 SHRs developed intracranial tumours (30%), at 648 days old on average, or 1.8 years. Of these tumours, 77% were located on the ventral aspect of the brain at the suprasellar region (average volume of 227.7 mm^3), 11% were located on the superior aspect of the cerebellum (495.2 mm^3), and 11% were documented in multiple locations (suprasellar with brain infiltration, 30% of total average coronal section area, 284.9 mm^3 in volume). Suprasellar tumours had a reticulin-positive monomorphic sheet-like or insular-like cellular pattern, with eosinophilic cytoplasm, round to oval nuclei with salt and pepper chromatin, low mitotic activity, and stromal capillary networks. Taken together, evidence so far indicates a neuroendocrine tumour sub-type, but ongoing analyses of other targets remain. **Discussion/Conclusion:** Estimates of lifetime intracranial tumour incidence in other common laboratory rodent strains, such as Sprague-Dawley, Fischer, and Wistar rats, range from 0.5-5%. The comparatively high intracranial tumour incidence rate in our sample suggests that aged SHRs have a greater susceptibility to intracranial tumours versus other laboratory rodent strains, though this requires further investigation. Caution and enhanced monitoring are warranted when using very old SHRs in cardiovascular research to ensure their welfare.

Disclosures: A.C.J. Kalisvaart: None. **F.K.H. van Landeghem:** None. **C. Wilkinson:** None. **F. Colbourne:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

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Topic: B.11. Neuro-Oncology

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Shanghai Municipal of Science and Technology Project (20JC1419500)

Title: Dura macrophages bypass cerebrospinal fluid barrier to drive leptomeningeal metastasis progression

Authors: *J. ZHAO[1], Y. CHI[2];
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Abstract: Leptomeningeal metastasis (LM) is a devastating complication characterized by the infiltration of cancer cells into leptomeninges and the cerebrospinal fluid (CSF). The prognosis of LM is dire with a grim survival of few months, and little progress has been made in improving survival outcomes. The immense number of myeloid cells at CSF barrier provide constant surveillance in the CSF and meningeal space, responsible for maintaining brain homeostasis. However, the myeloid cells have lost their function in controlling LM development, and the underlying mechanism by which tumor cells evade immune surveillance remains poorly understood, posing a significant challenge for the development of effective treatments. Here, we utilize genetic fate-mapping, longitudinal two-photon time-lapse imaging, and single-cell profiling technologies to investigate the precise origin, cellular crosstalk, and molecular landscape of macrophages that inhabit the CSF barrier and contribute to LM progression. Mechanically, we find that LM-associated macrophages (LAMs) originate locally from the dura mater, migrating into the CSF niche via a matrix metalloproteinase 14 (MMP14)-dependent manner. Further, we also identify the CSF-resident LAMs critically require the presence of secreted phosphoprotein 1 (SPP1) for their establishment and recruitment, leading to an immunosuppressed microenvironment. Conversely, suppression of the SPP1-MMP14 pathway via genetic or pharmacological interventions, which blocks the migratory capability of macrophage bypassing CSF barrier, can impede cancer cell proliferation and improve survival in LM mouse models. Together, our findings reveal a private source for LM-associated innate immunity within the meningeal space and supply the potential targets of immunotherapeutic interventions for LM.

Disclosures: J. Zhao: None. **Y. Chi:** None.

Poster

PSTR255. Glioblastoma and Other Nervous System Cancers: Mechanisms and Techniques

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.27/D49

Topic: F.04. Neuroimmunology

Support: NIH, NIGMS 1R35 GM118182
NIH, NIGMS R01GM132672

Title: Nucleus Tractus Solitarii-specific activation by Tumor Necrosis Factor

Authors: *S. PETRUZZELLI[1], S. S. CHAVAN[2], K. J. TRACEY[2];
[1]Feinstein Inst. for Med. Res., Manhasset, NY; [2]Feinstein Inst. For Med. Res., Feinstein Inst. For Med. Res., Manhasset, NY

Abstract: The inflammatory responses to infection and injury are tightly controlled by neural reflex mechanisms. Proinflammatory cytokines (such as TNF) produced by immune cells during infection and injury, and other inflammatory mediators have been shown to activate sensory signaling in the vagus nerve. However, it remains unclear whether the brain encodes cytokine-specific information. Here, we develop methods to map the neuronal populations in the Nucleus Tractus Solitarii (NTS), a brainstem nucleus that receives sensory input from the vagus nerve. Transgenic targeted-recombination-in-active-populations (TRAP2) mice that expressed tamoxifen-inducible Cre under control of an activity-dependent c-Fos promoter were crossed with a Cre-dependent tdTomato reporter line. These mice (TRAP2/tdTomato mice) were injected with 4-OHT (an active form of Tamoxifen) to induce Cre recombination and tdTomato expression. 30 min later, TNF was administered intraperitoneally to these mice. One week after initial TNF challenge, mice were re-challenged with TNF, and brains were harvested 2 h post for c-Fos immunostaining. Administration of TNF induces increased tdTomato expression (representing increased neuronal activity) in specific neuronal populations in the NTS. Re-challenging with TNF on day 7 revealed that a significant number of neurons TRAPed on day 0 (expressing tdTomato) are reactivated (tdTomato+ and c-Fos+) on day 7. Statistical analysis on double positive data shows a significant difference between the experimental and the control groups ($p= 0.0159$). In addition, re-exposure of mice to TNF results in the recruitment of additional neuronal populations in the NTS, as labeled by cFos only. A population of TNF-responsive neurons is found to be localized in the central and intermedial subnuclei within the NTS. Together, these studies reveal that the TNF-specific information is encoded in the brainstem NTS region.

Disclosures: S. Petruzzelli: None. **S.S. Chavan:** None. **K.J. Tracey:** None.

Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.01/D50

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: German Research Foundation (CRC 1182 ”Origin and Function of Metaorganisms
EXC 2167 “Precision Medicine in Chronic Inflammation
RU 5042 “miTarget"
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German Research Foundation for the Clinician Scientist Program in Evolutionary Medicine (CSEM)
Medical Faculty University of Kiel

Title: Disease and stage specific alterations of the oral and fecal microbiota in Alzheimer’s disease

Authors: S. PHILIPPEN[1], A. TROCI[2], P. RAUSCH[2], J. RAVE[1], G. WEYLAND[1], K. NIEMANN[1], K. JESSEN[1], A. FRANKE[2], C. BANG[2], ***T. BARTSCH**[1];
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Abstract: The microbiota in the human gastrointestinal tract has been suggested to influence the etiopathogenesis of Alzheimer’s disease (AD). Although alterations in the gastrointestinal microbiome of AD patients have been reported, little is known about the microbiome in different stages of the disease.
Here, we used 16S rRNA analysis of fecal and oral samples from patients with AD and mild cognitive impairment (MCI) (n=84), a group of healthy adults with high-risk genotype (APOE4, n=17) and healthy sex- and age-matched controls (n=50) to characterize the microbial communities in the gut and the oral cavity. We further investigated the relationship of the microbial composition to Alzheimer’s disease specific biomarkers in the cerebrospinal fluid (CSF).
Results show the diversity of the fecal microbial communities to be slightly decreased in the patient cohort and differences in bacterial abundances are identified including Bacteroidetes, Ruminococcus, Sutterella, Porphyromonadaceae. In contrast, the diversity of the oral microbiome is increased in AD patients and at-risk individuals and significantly higher abundance of gram-negative pro-inflammatory Porphyromonas and members of the Proteobacteria, especially Haemophilus, Neisseria and Actinobacillus are observed in the oral microbiota of AD and MCI patients. The abundance of theses dominant bacteria correlates with the CSF biomarker of AD.
The findings show a shift in the microbial composition of AD patients which is already detectable in prodromal stage of MCI. In case of the oral microbiome, alterations are already dominant at the stage of individuals at risk. Altogether, this indicates stage-dependent alterations of the microbial composition in AD pointing towards a bacterial milieu facilitating systemic inflammation which might enhance neuroinflammation and neurodegeneration. Further investigations are needed to understand the dynamics of microbiome changes in the course of AD and its impact of the neurodegeneration in Alzheimer’s disease.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.02/D51

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fondecyt 1200880
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Fondecyt 1230170
ANID FOVI 220134

Title: The retina of Octodon degus: A natural model for studying biomarkers associated with diabetes during aging.

Authors: D. NEIRA[1], D. PONCE[1], M. ESCOBAR[3], P. REYES[3], F. MIQUELES[3], C. IBACETA-GONZALEZ[4], J. PORTAL[3], J. MINONZIO[2], J. ARAYA[5], ***A. G. PALACIOS**[1]; [1]Neurosci., [2]Ingeniería Informatica, Univ. de Valparaiso, Valparaiso, Chile; [3]Electronica, Univ. Federico Santa Maria, Valparaiso, Chile; [4]Inst. de Psychiatrie et Neurosciences de Paris, Paris, France; [5]Escuela de Tecnología Médica, Facultad de Salud, Univ. Santo Tomas, Santiago, Chile

Abstract: The Octodon degus, a native rodent from South America, naturally exhibit insulin resistance, positioning it as a valuable animal model in studying the pathophysiology of diabetes mellitus. In our study, young degus (YD, n=4) and adult degus (ADC, n=6) and without cataracts (AD, n=6), were housed under bioethical certification in the animal facility at the Universidad de Valparaiso. These animals underwent retinal physiological evaluations using multi-electrode experiments (252 channels, 20 KHz) from where we measured the micro electroretinogram (µERG), a measure of evoked visual potential to monitor both age-related physiological changes associated with cataracts. For the µERG a-wave response, indicative of photoreceptor activity, the AD group presented a higher at 867±343 µV ON-flash response amplitude compared to 570±293 µV for the YD group and 429±138 µV for the ADC group. In the case of the µERG b-wave response, associated with on-bipolar cell activity, the AD group also demonstrated a higher amplitude of 282±163 µV relative to the YD group 223±98 µV and the the ADC group with the lowest amplitude of 153±59µV ($p<0.0001$). Assessing the OFF-flash response, the amplitude for the µERG a-wave was 228±105 µV for AD, 184±50 µV for YD, and 209±88 µV for ADC. The µERG b-wave showed amplitudes of 602±263 µV for AD, 369±113 µV for YD, and 399±238 µV for ADC. In terms of the cut-off frequency response was highest for the ADC group at 5.0±1.2 Hz, compared to 3.8±0.4 Hz for YD and 3.6±0.5 Hz for ODC ($p<0.001$). An additional

indicator of retinal health status, the receptive field (RF) estimate was determined using a Stimuli Trigger Average (STA). The size of the RF was found to increase in AD degus compared to YD and ADC; displaying diameters of 168.46±70.95 µm, 136.58±29.13 µm, and 128.22±37.20 µm, respectively (mean±SD, $p<0.0001$). Data were analyzed using a two-way ANOVA followed by Tukey's multiple comparisons test for determining statistical significance. In summary, the retinal visual responses and RF characteristics of degus are influenced by age and cataract development. Further investigations are warranted in older degus to elucidate other potential age-related biomarkers.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.03/D52

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NC3Rs Studentship NC/T002018/1

Title: An improved Caenorhabditis elegans model of alzheimer's disease to monitor neuronal signalling activity

Authors: *V. BAJUSZOVA, N. COHEN, J. JOHNSTON;
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Abstract: Alzheimer’s disease (AD) is the most prevalent form of neurodegenerative disease, characterised by the presence of Aβ plaques and neurofibrillary tangles, mediating memory impairments due to loss of neurons and impairments in neuronal plasticity. The most common model to study the toxic effects of Aβ in AD are transgenic rodents. However, these animals develop cognitive impairments making them suffer. Thus, to reduce and replace the rodent animals used to study these toxic effects, we are developing a *C. elegans* neuronal model of human $A\beta_{1-42}$. Existing Aβ transgenes available for *C. elegans* have fluorescent markers in or near the head preventing functional imaging of neural activity. To overcome this we have created a human $A\beta_{1-42}$ *C. elegans* strain that has a fluorescent co-injection marker in the posterior intestine. As glutamatergic signalling is one of the neuronal subtypes largely affected in AD, we are also generating constructs containing a glutamate and calcium sensor for imaging glutamatergic activity in all glutamatergic neurons and a subset of glutamatergic neurons. Expression of these constructs in the newly generated Aβ strain will allow simultaneous glutamate and calcium imaging to determine the onset of glutamatergic signalling defects and the subtype of glutamatergic neurons affected first.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.04/Web Only

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Medical Research Council Doctoral Training Partnership PhD scholarship to K.P.G. and K.C. from King's College London
(PGC2018-094307-B-I00) funded by MCIN/AEI/10.13039/501100011033

Title: Multi-spine boutons, memory, and Alzheimer's disease

Authors: *R. MARTINEZ[1], I. V. KRAEV[2], L. ALONSO-NANCLARES[3], J. DEFELIPE[4], K. K. CHO[1], P. GIESE[1];
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Abstract: Synaptic changes are thought to underlie learning and memory, with synapse loss being considered the best correlate of memory impairment in Alzheimer's disease (AD). Multiple synapses, such as multi-spine boutons (MSBs), have been linked to learning and memory, however their role is poorly understood, and they are often overlooked in AD research. We have used 3-dimensional electron microscopy, which provides sufficient resolution to unequivocally identify and classify established synapses, to address whether MSBs are affected by memory formation in a mouse model, and if MSBs change in post-mortem AD brain. MSBs account for 20% of all synapses in mouse CA1 stratum radiatum, and their abundance does not change after contextual fear conditioning (CFC). However, CFC decreases the number of synapses per MSB, hence their complexity (n=3-5). Further, AD does not change the abundance of MSBs in transentorhinal cortex and stratum pyramidale, but their complexity is increased (n=3-6). Please note that in these brain regions, synapse number is conserved after CFC and in AD, respectively. Our results suggest that changes in MSBs complexity occur in AD brain, which are the opposite of learning-induced alterations in MSB complexity. The decreased MSB complexity seen after CFC may be needed for memory retrieval, therefore the increased complexity seen in AD is expected to impair memory, most likely the retrieval process, as too many neurons become inter-connected. The role of MSB's in memory will be further investigated by analysing MSB number and complexity in the APP PS1 mouse model of AD.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.05/D53

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH BRAIN Initiative 1R01NS118442-01
Brightfocus Foundation Standard Award Program in Alzheimer's Disease Research (29225)

Title: Tau-mediated neurodegeneration disrupts emergent dynamics but not single neuron activity across sleep-wake states and cell types in a mouse model of tauopathy

Authors: *J. MCGREGOR[1], C. A. FARRIS[1], S. ENSLEY[1], Y. LIU[1], T. TU[1], K. RONAYNE[1], C. WANG[1], R. WESSEL[1], E. L. DYER[2], D. M. HOLTZMAN[1], K. B. HENGEN[1];
[1]Washington Univ. in St. Louis, St. Louis, MO; [2]Georgia Inst. of Technol., Atlanta, GA

Abstract: Neuronal activity is homeostatically-regulated around set-points of activity at the level of individual neurons and at the level of neuronal networks. These processes are thought to stabilize brain function across sleep-wake states, aging, and in response to perturbations. In the context of neurodegenerative disease, it is likely that these homeostatic mechanisms compensate for perturbations caused by toxic proteins, and only when these mechanisms are overwhelmed do neural dynamics become disrupted and symptoms emerge. However, it is unclear how neuronal activity is regulated around set points in the context of neurodegeneration. We performed chronic, multi-month electrophysiological recordings of ensembles of single units in CA1 of freely behaving wild-type mice (WT) and P301S/E4 mice (TE4), which are a mouse model of tauopathy. We found that the mean firing rate and coefficient of variation of interspike intervals (CV of ISIs) of individual neurons did not significantly differ between genotypes at any age, even late in the disease process. On the other hand, a homeostatic set-point of emergent properties of network dynamics (criticality) was significantly different between genotypes as a function of disease progression. We then developed a machine learning algorithm to automatically classify sleep-wake states from over 20,000 hours of extracted LFP data with an accuracy greater than 90%. We found that mean firing rates and CV of ISIs during wake, NREM, and REM did not significantly differ between genotypes at any age range, yet criticality was significantly altered across both wake and sleep states late in life. Further, we found that TE4 mice displayed a significant disruption of the natural sleep-wake cycle - one of the earliest known behavioral symptoms of neurodegenerative disease - which occurred at nearly the same age as the disruption in criticality. These results suggest that homeostatically-regulated set points of individual neuron activity remain remarkably stable across the sleep-wake cycle, age, and disease states, whereas set points of network activity are sensitive to disease states. The strong correlation between aberrant network activity and early symptoms of disease suggest that measures of network activity may serve as potential biomarkers.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR256.06/D54

Topic: C.02. Alzheimer's Disease and Other Dementias

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NIH K01 AG068366
NIH RF1 AG061774
NIH R21 MH125242

Title: Alteration of sleep oscillations and activity of hippocampal parvalbumin neurons in the 5XFAD mouse model of Alzheimer's disease

Authors: *F. KATSUKI, J. M. MCNALLY, D. GERASHCHENKO, R. E. BROWN; Psychiatry, VA Boston Healthcare System/Harvard Med. Sch., West Roxbury, MA

Abstract: Neuronal network dysfunction is one of the early characteristics of Alzheimer's disease (AD). Another early characteristic of AD is sleep abnormalities, including changes in overall sleep pattern and sleep oscillations such as slow wave (0.5-1 Hz) activity and sleep spindles (10-15 Hz). These abnormalities correlate with the severity of amyloid-β deposition and cognitive impairment at later stages of the disease. However, the relationship between the AD-related cortical network dysfunction and sleep abnormalities is poorly understood. Here, we investigated whether abnormal activity of hippocampal (HPC) parvalbumin (PV) containing neurons during the early stage of AD is relevant to impaired sleep oscillations and cognition. To assess this, we simultaneously performed fiber photometry recordings and local field potential (LFP) recordings in the AD mouse model at different ages.
We performed sleep recordings from 6 5XFAD/PV-cre mice (AD) and 4 control PV-cre mice (Ctr) using LFP electrodes in medial prefrontal cortex (mPFC) and HPC. The fiber photometry recordings were performed in the contralateral side of HPC to identify and record activity of PV neurons in the same mice. Recordings were performed for 24h each month at ages 3-6 months-old (mo). To detect relevant signals in the photometry data, we computed a peak prominence value for each peak in the data and identified those which exceeded a threshold as the prominent peaks. The spontaneous Y-maze alternation task was performed to assess cognition.
The proportion of REM sleep during the 12h light (inactive) phase was significantly lower in the AD mice at 6 mo compared to 3 mo (paired t-test: $p=0.03$). NREM spindle density during the light phase in mPFC was significantly lower at 6 mo in AD mice (paired t-test: $p=0.01$). Decreased slow wave (SW) density (paired t-test: $p=0.01$) and SW-spindle coupling density (paired t-test: $p=0.008$) in HPC were also found at 6 mo in AD mice, while no significant changes were observed in Ctr mice. In fiber photometry data the proportion of prominent peaks detected in HPC PV neurons was decreased in AD mice at 6 mo. The % change in prominent peaks from 3 to 6 mo showed a significant correlation with % change in mPFC spindle density

(r=0.71, p=0.02). Although some AD mice showed a decline in Y-maze performance at 6 mo, the difference was not statistically significant.
The results suggest that changes in activity of HPC PV neurons might be linked to sleep oscillation changes in AD mice. Cognitive decline was not as robust at 6 mo, suggesting that changes in sleep and PV neuron activity observed here could be characteristics of earlier stages of AD before apparent cognitive impairment.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

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Program #/Poster #: PSTR256.07/D55

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 1R21AG075807-01A1
Japan Agency for Medical Research and Development

Title: Donor Mouse-derived Interneuron Progenitors Rescue Host Circuit Function in an Alzheimer's Model

Authors: *S. YOKOMIZO[1], M. MACI[1], M. MILLER[1], S. AYGAR[1], D. VOGT[2], J. R. NAEGELE[3], K. KASTANENKA[1];
[1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Michigan State Univ., Michigan State Univ., Grand Rapids, MI; [3]Wesleyan Univ., Wesleyan Univ., Middletown, CT

Abstract: The number of Alzheimer's disease (AD) patients continues to escalate annually. Alzheimer’s patients are starting to gain access to FDA-approved disease-modifying therapies. However, those come with major risks and hence additional therapeutic strategies are needed. Sleep impairments have been identified in addition to memory deficits in Alzheimer’s patients. Disruptions of sleep-dependent brain rhythms, slow oscillations, prevalent during NREM sleep were observed in patients with AD as well as in the mouse models, including APP/PS1 mice. Reduced slow wave power was due to the dysfunction of GABAergic interneurons and low GABA. Thus, we hypothesized that transplantation of healthy Medial Ganglionic Eminence (MGE) inhibitory interneuron progenitors could restore inhibition and rescue cortico-thalamic circuit function driving slow oscillations in APP/PS1 hosts. To that end, healthy donor MGE progenitors were harvested from VGAT-Venus or VGAT-ChR2-EYFP mice and were transplanted into the cortices of host APP/PS1 mice. The viability, maturation, and differentiation of the transplanted donor MGE progenitors were assessed via immunohistochemistry. Furthermore, to determine the functionality of donor inhibitory neurons and their effect on slow oscillations, voltage-sensitive dye imaging was conducted 2 months post-transplantation once the donor cells had time to mature and incorporate into host circuitry.

Furthermore, light activations of ChR2 in APP/PS1 mice transplanted with VGAT-ChR2-EYFP cells were undertaken to measure the effect of optogenetic stimulation on slow oscillations. We found that the transplanted MGE progenitors not only survived but also differentiated into mature interneurons expressing somatostatin and parvalbumin markers within the host mice. Importantly, transplantation of healthy MGE progenitors restored the slow wave power in APP/PS1 mice 2 months post-transplantation. Optogenetic activation of donor interneurons further increased the power of slow oscillations. These results suggest that stem cell therapy with MGE progenitors warrants further investigation and could hold promise as a therapeutic strategy to combat the progression of Alzheimer's disease.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR256.08/D56

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: tlanta VA Medical Center Collaborative Research Award
NIH/NIA AG067473

Title: Identification of vulnerable brain circuits in a mouse model of Alzheimer’s disease using diffusion tensor MRI imaging

Authors: Y. LI[1], D. TAKASHIMA[1], S. POURKHODADAD[1,3], M. Q. JIANG[1,3], K. HEKMATYAR[5], K. BERGLUND[2,3], ***L. WEI**[1], J. YANG[5], S. YU[1,4];
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Abstract: N-methyl-D-aspartate receptors (NMDARs) are primary mediators of Ca^{2+} influx into excitatory neurons. According to the Ca^{2+} hypothesis, hyperactivity of NMDARs and excitatory neurons is an initial and chronic pathogenic mechanism of late-onset sporadic AD and related dementia (ADRD). We identified that GluN3A(NR3A), a negative regulatory subunit of NMDARs, is critical for Ca^{2+} homeostasis while its deficiency is a genetic factor contributing to NMDAR-mediated degenerative excitotoxicity and the development of AD/ADRD. Aging GluN3A knockout (KO) mice exhibited moderate but persistent neuronal hyperactivity, elevated intracellular Ca^{2+}, and neuronal loss, accompanied by age-dependent olfactory deficit and psychological/cognitive dysfunctions as well as amyloid/tau pathology. In this study, we use diffusion tensor imaging (DTI) to determine the selective vulnerability of associated neuronal connections between the olfactory system, the vision system, and the hippocampus, which are

critical for sensory memory. The DTI analysis yields valuable phenotypical information, such as early regional atrophy, and quantitative biomarkers that can be analyzed within the context of networks. Ex vivo MR images of all isolated brains were acquired on the 7-T MRI system, using a 4-channel mouse array coil. The brains are fixed in 4% PFA solution before transferring to a Fomblin solution. After insertion of the containing tube in the coil and optimizing the magnet, a high-resolution 3D T2 weighted RARE anatomical scan and a high-resolution DTI scan at the same resolution as T2 were performed on each brain. The DTI scan was processed for fiber tracking analysis and the network connectivity between interested regions was performed. The significance of network connectivity lies in its ability to integrate microstructural effects, such as neurodegeneration of gray and white matter or toxicity associated with Ca^{2+}-mediated degenerative excitotoxicity. The volume derived from DTI scan revealed significant reductions of the olfactory bulb and superior colliculus. Moreover, tractography determined markedly decreased neuronal tract numbers between the olfactory bulb and the hippocampus for olfactory memory as well as between the superior colliculus and lateral geniculate nucleus for vision function in the aging GluN3A KO brain. The analysis of brain connections including the volume of specific structures and neuronal tracks provides insight into network aberrations during the progression of this sporadic AD/ADRD model.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.09/D57

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: European Research Council: ERC-CoG-2020-101001916
Spanish Ministry of Economy and Competitiveness: PID2020-113007RB-I00, SAF-2017-82185-R and RYC-2015-171899
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Secretaria de Educación, Ciencia Tecnología e Innovación (SECTEI) of the Regional Government of Ciudad de México: SECTEI/159/2021

Title: Alzheimer's disease triggers unusual structural plasticity in human dentate granule cells

Authors: *B. MÁRQUEZ-VALADEZ[1,2,3,4], A. RABANO[5,6], M. LLORENS-MARTÍN[1,2,3,4]; [1]Neurophatology, Ctr. de Biología Mol. “Severo Ochoa”, Madrid, Spain; [2]Spanish Res. Council (CSIC), Madrid, Spain; [3]Univ. Autónoma de Madrid (UAM), Madrid, Spain; [4]Ctr. for Networked Biomed. Res. on Neurodegenerative Dis. (CIBERNED), Madrid, Spain; [5]Carlos III Inst. of Hlth., Carlos III Inst. of Hlth., Madrid, Spain; [6]Neurophatology, CIEN Fndn., Madrid, Spain

Abstract: Alzheimer´s disease (AD), the most common form of dementia in industrialized countries, severely targets the hippocampal formation in humans and mouse models of this condition. The adult hippocampus hosts the continuous addition of new dentate granule cells (DGCs) in numerous mammalian species, including humans. Although the morphology and positioning of DGCs within the granule cell layer (GCL) match their developmental origin in rodents, a similar correlation has not been reported in humans to date. Our data reveal that DGCs located in inner portions of the human GCL show shorter and less complex dendrites than those found in outer portions of this layer, which are presumably generated developmentally. Moreover, in AD patients, DGCs show early morphological alterations that are further aggravated as the disease progresses. An aberrantly increased number of DGCs with several primary apical dendrites is the first morphological change detected in patients at Braak-Tau I/II stages. This alteration persists throughout AD progression and leads to generalized dendritic atrophy at late stages of the disease. Our data reveal the distinct vulnerability of DGCs located in the inner and outer portions of the GCL to AD and support the notion that the malfunction of the hippocampus underlies cognitive impairments in patients with AD.

Disclosures: B. Márquez-Valadez: None. **A. Rabano:** None. **M. Llorens-Martín:** None.

Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR256.10/D58

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1AG063837
NIH Grant RF1AG078340

Title: Alzheimer's disease amyloid-beta oligomers effect on behavior, cognition, and affect in rhesus monkeys

Authors: *M. G. BAXTER[1], J. CHARBONNEAU[2], S. B. CARP[2], J. BENNETT[3], G. MOADAB[3], S. P. OTT[2], P. H. RUDEBECK[5], J. H. MORRISON[4], E. BLISS-MOREAU[3]; [1]Section on Comparative Med., Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [2]California Natl. Primate Res. Ctr., [3]California Natl. Primate Res. Ctr. and Dept. of Psychology,

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Abstract: Amyloid-beta oligomers (AβOs) are thought to initiate a pathological cascade that leads to Alzheimer's disease in humans. We have previously shown (Beckman et al., 2019, PNAS) that one month of treatment of rhesus monkeys with synthetic AβOs leads to neuroinflammation and reductions in thin dendritic spines in dorsolateral prefrontal cortex. This phenotype resembles accelerated cortical aging, which may set the stage for vulnerability to developing Alzheimer's disease. The consequences of AβO treatment on brain function in this model are not known. We tested male and female rhesus monkeys on a battery of behavioral, cognitive, and affective tasks. Testing included spatiotemporal working memory (delayed response), visual recognition memory (delayed nonmatching-to-sample), 24-hour activity levels in the home environment, affective reactivity (human intruder test and object reactivity), and autonomic responses to affective videos. Individuals carrying out testing and scoring of behavioral data are blinded to treatment condition. Following completion of training, monkeys then received 9 weekly infusions into the lateral ventricle of AβOs derived from postmortem brains of humans with Alzheimer's disease (N = 5), or control material that was identical except for the immunoprecipitation of AβOs out of the infusate prior to infusion (N = 4). Monkeys experienced a decrease in locomotor activity during the infusion period relative to pre-infusion baseline. This decrease was attenuated in the AβO group, perhaps reflecting increased locomotor activity associated with the development of neuroinflammation. Retesting on all cognitive and affective tasks will occur after infusions are complete and will provide insight as to whether the AβO infusions adversely impact these domains. Following the behavioral assessments, the monkeys will be perfused and analyzed for cellular and synaptic reflections of neuropathology. These data will provide direct evidence on whether pathological sequelae of AβO administration in rhesus monkeys are accompanied by impairments in cognition and affect that are characteristic of individuals in the early stages of Alzheimer's disease, potentially validating this as a novel nonhuman primate model of early Alzheimer's pathogenesis.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.11/D59

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministry of Education Tier 3 Research Fund (MOE2017-T3-1-002)
National Medical Research Council (MOH-000962)

Title: Complex effects of age, sex, and Alzheimer’s Disease on hippocampal spatial coding

Authors: *R. LONG[1], Y. FANG[3], G. J. AUGUSTINE[4], S.-C. YEN[2];
[1]N.1 Inst. of Hlth., [2]Engin. Design and Innovation Centre, Col. of Design and Engin., Natl. Univ. of Singapore, Singapore, Singapore; [3]Ageing Res. Inst. for Society and Education, Interdisciplinary Grad. Programme, [4]Lee Kong Chian Sch. of Med., Nanyang Technological Univ., Singapore, Singapore

Abstract: Encoding of spatial memory in the human hippocampus is impaired during aging and in Alzheimer's disease (AD), with women being more susceptible to AD than men. However, the interactions between age, sex, and AD remain poorly understood. We compared spatial coding in wild-type (WT) mice and in an AD model mouse with three human AD-related APP mutations (APP-TKI; Nature Neurosci. 17: 661). *In vivo* two-photon calcium imaging was used to measure the activity of hippocampal CA1 neurons while the animals traversed a 220-cm treadmill. The effects of aging, AD, and sex on spatial coding were examined in both genotypes by comparing young (3–8 months) and old (17–24 months) animals of both sexes. Dimensionality reduction (Isomap) was used to represent neural population activity as manifolds and a linear mixed-effects model was used to test the significance of effects. Age affected the mean curvature of these manifolds ($d = 1.57$, $p < 0.01$). For old mice, both AD ($d = -1.38$, $p < 0.05$) and sex ($d = -1.89$, $p < 0.01$) significantly affected the mean curvature, with a significant interaction ($d = 3.13$, $p < 0.05$) between them. We also characterized manifold topology by using persistent homology, specifically focusing on the properties of 1-dimensional homologies (H1). For the rank of H1, which signified the number of 1-dimensional holes in the manifold, there was a significant age effect ($d = 1.38$, $p < 0.01$). For old mice, there was a non-significant AD effect ($d = -0.834$, $p = 0.076$), a significant sex effect ($d = -1.32$, $p < 0.01$), and a significant AD and sex interaction ($d = 1.78$, $p < 0.05$). Furthermore, age significantly affected the length of the longest H1 interval ($d = -1.49$, $p < 0.01$), which captured the continuity of the longest uninterrupted segment of the manifold. For old mice, both AD ($d = 1.77$, $p < 0.01$) and sex ($d = 2.29$, $p < 0.01$) had a significant effect, with significant negative interaction between AD and sex ($d = -4.05$, $p < 0.01$). In summary, old female APP-TKI mice had more severe spatial memory impairment than their male counterparts. Surprisingly, this trend was reversed in the WT mice, with the old male mice exhibiting greater spatial memory impairment than old female mice. Our overall findings suggest that sex differences play a major role in both aging-related and AD-related impairment of spatial memory coding.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.12/D60

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Hyperexcitability of interneurons is causally involved in early neuronal network dysfunction and memory impairment in APP/PS1 mice

Authors: *M. ABDOLLAHI NEJAT[1], S. HIJAZI[2], A. B. SMIT[1], R. E. VAN KESTEREN[1]; [1]Dept. of Mol. and Cell. Neurobiology, Ctr. for Neurogenomics and Cognitive Res., VU Univ. Amsterdam, Amsterdam, Netherlands; [2]Dept. of Pharmacol., Univ. of Oxford, Oxford, United Kingdom

Abstract: Imbalances in neuronal networks resulting from alterations in both the excitatory and inhibitory signaling pathways are thought to play a role in the pathogenesis of Alzheimer's disease (AD). Here, we contribute to the growing evidence of neuronal network dysfunction as an early symptom in AD by highlighting alterations in specific inhibitory interneurons in the hippocampus CA1 of APP/PS1 mice, a mouse model for amyloidosis. Specifically, we show that both hippocampal parvalbumin (PV) and somatostatin (SST) interneurons are hyperexcitable at an age of ~16 weeks, while pyramidal neuron excitability remains unaltered. The hyperexcitable state of these interneurons is concurrent with increased inhibitory transmission onto hippocampal pyramidal neurons and coincides with impairments in spatial learning and memory. Interestingly, hippocampal PV interneurons exhibit a biphasic response, becoming hypoexcitable at ~24 weeks of age, while SST interneurons remain hyperexcitable. Our previous work shows that early intervention aimed at preventing PV interneurons from becoming hyperexcitable not only restores alterations in PV interneuron excitability in the short-term, but also has long-term beneficial effects on memory and hippocampal network activity. We now show that also early intervention targeted at restoring SST interneuron activity results in long-lasting restoration of SST interneuron excitability. Interestingly, targeting SST interneurons also rescued PV interneuron function on the long term. These findings suggest that the imbalances in hippocampal neuronal networks observed in AD may involve the dysfunction of multiple inhibitory interneurons, and that early intervention targeted at restoring interneuron activity could have clinical implications in terms of preventing memory decline.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR256.13/D61

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R21AG067008-01
NIH Grant R01MH099073
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NRF-2021R1A6A3A01086526

Title: Aberrant coding patterns in the prefrontal-hippocampal circuit during naturalistic risky decision-making in a mouse model of Alzheimer's disease

Authors: *E. KIM[1], S. PARK[3], B. P. SCHUESSLER[4,5], H. BOO[1], J. CHO[3], J. J. KIM[1,2]; [1]Psychology, [2]Program in Neurosci., Univ. of Washington, Seattle, WA; [3]Brain and Cognitive Sciences, Scranton Col., Ewha Womans Univ., Seoul, Korea, Republic of; [4]VA Northwest Geriatric Res. Educ. and Clin. Ctr., [5]VA Northwest Mental Illness Research, Education, and Clin. Ctr., VA Puget Sound Hlth. Care Syst., Seattle, WA

Abstract: The focus of basic research on Alzheimer's disease (AD) using animal models has predominantly centered on neuropathological markers and memory loss. However, there remains a significant gap in our understanding of how AD distinctly affects the neural circuit mechanisms underlying risky decision-making. This study aimed to investigate how the presence of amyloid pathology affects risky foraging decisions and prefrontal-hippocampal circuit activity in a mouse model of AD. To achieve this, five familial AD (5XFAD) and wild-type (WT) mice (4-9 mos old) were subjected to a naturalistic 'approach food-avoid predator' paradigm, adapted from Kim et al. (2016). Animals implanted with tetrode arrays in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC; targeting the CA1 subregion) ipsilaterally went through successive stages of nest habituation, baseline foraging, and predator testing in a T-shaped maze with two different pellets in each arm (grain-based vs. chocolate-flavored). Neural activities were recorded during the predator testing, which consisted of successive pre-predator, predator, and post-predator stages. During the predator trials, each time the animal approached the preferred pellet, a predator (a puppet eagle on wheels) surged forward via a linear actuator, while no predator was present on the non-preferred pellet side. In response to the predator, the WT mice switched their foraging strategy from preferred to non-preferred pellets. In contrast, the 5XFAD mice continued to choose their preferred pellets at a high rate, indicating an inability to adjust their foraging behavior flexibly in the face of threats. The WT mice showed threat distance-dependent stability of dHPC place cells between the pre-predator and predator sessions, while the 5XFAD mice displayed comparable levels of session-by-session spatial correlations across the place field locations. At the risky decision point, the proportion of synchronous dHPC-mPFC cell pairs decreased in 5XFAD mice compared to the WT group. Following predator encounters, 5XFAD mice exhibited decreased and shortened dHPC sharp-wave ripple activity compared to the WT mice. However, both WT and 5XFAD mice displayed comparable post-shock and contextual freezing in a contextual fear conditioning paradigm, indicating that unconditioned and conditioned fear levels remained intact in 5XFAD mice. These findings suggest that the impairments in risky decision-making in AD might stem from abnormal interregional neuronal interactions between the dHPC and mPFC.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.14/D62

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1AG065675
NIH Grant RF1MH120020

Title: Monosynaptic Rabies Viral Tracing Reveals Subiculum Circuit Connectivity Alterations in Alzheimer's Disease

Authors: *Q. YE, G. GAST, E. G. WILFLEY, H. HUYNH, C. HAYS, X. XU;
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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly and causes progressive memory and behavioral impairment. Examining the changes in neural circuitry using AD model mice is an emerging strategy for a better understanding of AD neural mechanisms toward discovering new therapeutic targets. Our recent work indicates the disruption of long-range and local neural circuit connections in the hippocampus using an AD mouse model. The subiculum is the major output structure of the hippocampus and is among the earliest AD-impacted brain regions. We hypothesize that age-progressive alterations also occur in the neural circuit organization of the subiculum in the 5xFAD mouse model. To comprehensively map cell-type-specific circuit inputs, we utilized the novel viral-genetic tool of monosynaptic rabies tracing. We quantitatively assessed and compared the circuit connectivity of subiculum excitatory neurons in age-matched C57BL6 control and 5xFAD model mice at young and middle ages (3-4 months vs 8-9 months) in both sexes. The major subiculum input brain regions mapped by rabies tracing include hippocampal subregions, medial septum and diagonal band (MS-DB), subiculum (SUB), post subiculum (post SUB), visual (VIS) cortex, auditory (AUD) cortex, entorhinal cortex (EC), thalamus, and temporal association cortex (TeA). Our results reveal significant alterations in local and long-range circuit connections to the subiculum in AD model mice. The overall brain-wide connectivity strengths of subiculum inputs in aged AD model mice are weaker than in wild type mice. There are significant age and sex differences in the connectivity strengths of multiple input regions, including the hippocampal CA1, CA2, MS-DB, thalamus, RSC, VIS, AUD, and TeA. Our work provides new insights into subiculum-directed neural circuit mechanisms during AD progression and supports neural circuit disruptions as a prominent feature of AD.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.15/D63

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01DC018650
AARF-22-970734

Title: Revealing hidden sensorimotor memories in mice with AD-relevant pathology

Authors: *A. SANTI, S. MOORE CORONA, A. WANG, J. LAWLOR BLONDEL, K. FOGELSON, K. KUCHIBHOTLA;
Johns Hopkins Univ., Baltimore, MD

Abstract: Memories must be accessible for them to be useful. Alzheimer's disease (AD) is a progressive form of dementia in which cognitive capacities slowly deteriorate due to underlying neurodegeneration. Interestingly, anecdotal observations have demonstrated that Alzheimer's patients can exhibit cognitive fluctuations during all stages of the disease. In particular, it is thought that contextual factors are critical for unlocking these hidden memories. To date, however, exploration of the neural basis of cognitive fluctuations has been hampered due to the lack of a behavioral approach in mouse models to dissociate memories from contextual performance. Our previous work demonstrated that interleaving 'reinforced' trials with trials without reinforcement ('probe' trials) in an auditory go/no-go discrimination task, allows us to distinguish between acquired sensorimotor memories and their contextual expression. Here, we used this approach, together with two-photon calcium imaging on behaving AD-relevant mice (APP/PS1+), to determine whether amyloid accumulation impacts underlying sensorimotor memories (measured using 'probe' trials) and/or contextual-performance (measured using 'reinforced' trials) in an age dependent manner. We found that, while contextual-performance was significantly impaired in 6-8mo APP/PS1+ mice compared to age-matched controls, sensorimotor memories were surprisingly intact. At later ages (12mo), however, APP/PS1+ mice began to show deficits in both domains suggesting a sequence where contextual performance degrades before the sensorimotor memories. Using two-photon imaging in the auditory cortex of 6-8mo APP/PS1+ mice, we found that the poor contextual performance was accompanied by network suppression, reduced stimulus selectivity, and aberrant behavioral encoding. Impairments were not due to peripheral hearing deficits (measured by auditory brainstem response) and were concentrated near Aβ plaques. Strikingly, these deficits were less apparent in probe trials, suggesting the sensorimotor memory trace remains intact. These effects were recapitulated with a reinforcement learning model in which deficits in contextual scaling and inhibition explain the observed effects. Taken together, these results suggest that Aβ deposition impacts the integration of behavioral signals that enable contextual performance before degrading the underlying sensorimotor memory, suggesting that modulating these circuits may hold promise to reveal hidden memories.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

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Program #/Poster #: PSTR256.16/D64

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1AG072507
NIH Grant R21AG070880

Title: Impaired long term potentiation of lateral entorhinal input to CA1 in 5xFAD mice

Authors: M. THANGAVEL, C. TIAN, I. REYES, *A. V. MASURKAR;
Dept. of Neurol., NYU Grossman Sch. of Med., New York, NY

Abstract: **Motivation/problem statement:** Alzheimer disease (AD) disrupts synaptic integrity and plasticity in CA1, with evidence primarily for CA3→CA1 inputs. How AD disrupts direct entorhinal cortex (EC) inputs to CA1 and their plasticity is understudied, despite its critical role in memory. Moreover, dysfunction of lateral EC (LEC) input is less clear, despite its relevance to early AD pathogenesis. Here we examined how amyloid impacts long-term potentiation (LTP) of LEC→CA1 input in a transgenic model of amyloidosis. **Methods:** Acute hippocampal slices were prepared from 5xFAD and WT mice (7-8 mo. old, M/F) in which LEC had been injected with an AAV expressing ChR2. Ex vivo recordings were achieved with blue LED light to excite LEC axons and an extracellular field electrode in *stratum lacunosum moleculare* (SLM) of distal CA1 to record field responses. Input-output curves were established using 25-100% LED power for field postsynaptic potentials (fPSP) and postsynaptic excitatory potentials (fEPSPs) with inhibition intact and blocked (GABAA: 2μm SR95531, GABAB: 1μm CGP55845), respectively. LTP of fPSPs and fEPSPs was elicited with LED stimulation after a 10” baseline using theta burst stimulation (TBS). Fluorescence immunohistochemistry (IHC) was performed in separate mice using antibodies to N-type calcium channels. **Results:** All results are based on n=3-8/sex/genotype. LEC fPSP input-output curves were similar in WT and 5xFAD mice across both sexes. In contrast, LEC fEPSP slope input-output curves were reduced only in female 5xFAD mice, by ~50% compared to WT. TBS induced a late-onset LTP of the LEC fPSP of similar amplitude in female WT and 5xFAD mice (30” onset, 60” peak ~28%). With inhibition blocked, LTP of the fEPSP was earlier in onset (5-10”) and reached a higher 60” peak (~35%) in WT female mice, whereas in 5xFAD female mice it remained late-onset and reached a lower 60” peak (~17%). IHC of N-type calcium channels showed reduced fluorescence in the SLM of female 5xFAD mice versus WT. **Conclusion:** In 5xFAD mice, the impact of amyloid on LEC→CA1 input is sex-dependent, with alterations in female mice suggestive of reduced LEC-driven excitation and inhibition that maintains net excitatory impact. This alteration impacts the LTP of LEC→CA1 excitatory input, in both its onset and overall amplitude. A reduction in N-type calcium channels in female 5xFAD mice may serve as a presynaptic mechanism for these findings.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR256.17/D65

Topic: C.01. Brain Wellness and Aging

Support: Packard Award in Science and Engineering
National Institutes of Health grant R01-NS-109226
Emory ADRC Research Education Component

Title: Frequency-specific and sex-specific effects of sensory stimulation in a female mouse model of Alzheimer's disease

Authors: *A. PRICHARD[1,2], T. FRANKLIN[1], M. GOODSON[1], V. SILLS[1], M. SERI[1], E. SNYDER[1], A. KHAN[1], V. BHAT[1], C. HE[3], A. SINGER[1];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Ctr. for Visual and Neurocognitive Rehabil., Atlanta Veterans Affairs, Atlanta, GA; [3]Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Beneficial and maladaptive neuroimmune responses play a key role in the progression of Alzheimer's disease. We have found that noninvasive audiovisual neurostimulation (flicker) has different neuroimmune effects depending on the frequency of light and sound stimulation, which could be useful to induce different neuroimmune responses in the context of Alzheimer's disease pathology. However, few studies have examined flicker's effects in healthy and transgenic female mouse models of amyloidoisis, despite the known sex-specific differences in Alzheimer's disease etiology and incidence. In male animals, flicker alters hippocampal microglia morphology, an indicator of microglia activity, in healthy and transgenic male mouse models of Alzheimer's disease. Audiovisual flicker at 40Hz also improves memory performance in male mouse models of Alzheimer's disease. We discovered that neuroimmune signaling, including NFkB and cytokines, plays a causal in flicker's effects on microglia morphology. Neuromodulators and neurotropic factors are also known to affect microglia function, however the role of these factors in flicker's effects remain unknown. Accordingly, we tested the hypothesis that flicker induces frequency-specific effects on behavior, microglia, and neuromodulators and neurotrophic factors that regulate microglia in female mice. We examined changes in microglia morphology as well as neuromodulators and neurotrophic factors in the hippocampus and prefrontal cortex following exposure to chronic (1hour/ day for 7 days) audiovisual flicker across frequency, sex, and the presence or absence of amyloid pathology. We found sex-specific and frequency-specific differences in microglia morphology compared to no stimulation, as well as behavioral differences based on flicker frequency in female mouse models of AD. These results provide evidence that flicker frequency-induced changes to neuropathology as well as memory performance are driven by frequency and are dependent on sex. We suggest that these results may guide the future optimization of flicker interventions for neurodegenerative disease in humans.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR256.18/D66

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Optogenetic 40 Hz stimulation of parvalbumin- and somatostatin-expressing interneurons synergistically generate gamma oscillations and induce behavioral changes in wild-type and Alzheimer's disease mice

Authors: *E. S. BRADY[1], P. HONMA[1], P. NAMBIAR[1], Y. QIU[1], S. SAILLET[1], J. J. PALOP[1,2];
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Abstract: Network hypersynchrony and alterations to neuronal oscillations begin to occur in the early stages of Alzheimer's disease, ultimately resulting in impaired cognition. Changes to gamma oscillations as a result of amyloid pathology have previously been identified, with research from our lab suggesting these alterations occur as a result of dysfunctional inhibitory neurotransmission. Both parvalbumin (PV)- and somatostatin (SST)-expressing interneurons are thought to contribute to the generation of gamma oscillations and there is evidence for both groups of interneurons being affected in mouse models of amyloidopathy. What is still to be elucidated is the relative contribution of PV- and SST-expressing interneurons to generating the gamma oscillation in awake *in vivo* recordings and the cell type-specific effects amyloid pathology has upon their function. Therefore, using wild-type and hAPP-J20 mice, we sought to answer these questions using a combination of *in vivo* electrophysiology in freely moving animals and optogenetics. Optogenetically exciting PV-expressing interneurons at 40 Hz reliably induced a 40 Hz gamma oscillation, whereas stimulating SST-expressing interneurons at the same frequency did not. Interestingly, simultaneous stimulation of both groups of interneurons using mice expressing channelrhodopsin in Lhx6+ cells resulted in a larger increase in gamma oscillation power than with PV alone, suggesting a synergistic relationship between these two groups of interneurons. We further explored the effects of Lhx6+ interneuron-induced gamma oscillations and found that this stimulation paradigm could bring about real-time changes in spontaneous behavior in the open-field, identified using a machine learning approach. Lastly, in hAPP-J20 mice we found that the ability of PV+ and Lhx6+ interneurons to generate 40 Hz gamma was impaired, resulting in a reduction in gamma oscillation power. Changes to the extracellular action potentials of both PV+ and Lhx6+ interneurons were identified as well as impairments in the coupling of these interneurons and their post-synaptic targets to the gamma oscillation. Taken together, these experiments highlight the synergistic relationship between PV- and SST-expressing interneurons in generating gamma oscillations and the susceptibility of this circuitry to Alzheimer's disease-associated pathology.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.19/D67

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant F31AG069496 to LMV
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Title: Entorhinal-hippocampal desynchronization in a mouse model of Alzheimer's disease pathology

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Abstract: Background: Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by progressive cognitive decline and memory loss. Impairments in spatial navigation and hippocampal function in AD are well established, but it is unclear whether these changes are driven primarily by local dysfunction, or by altered inputs, such as projections from medial entorhinal cortex (MEC). Methods: To understand how AD pathology alters entorhinal-hippocampal circuits, we used male and female 3xTg mice, which express mutations in APP, presenilin, and tau. We performed acute *in vivo* silicon probe recordings to simultaneously record local field potentials and single units from MEC and hippocampus. Head-fixed mice were trained to run on a virtual reality linear track and recordings were performed during active navigation. By recording in two age groups, we were able to compare neural activity before and after the onset of spatial memory impairments. Results: We find an early loss of theta synchrony between MEC and CA1 prior to cognitive decline in 6-month-old 3xTg mice compared to WT controls. This desynchronization suggests a loss of communication between these brain regions, even before the onset of spatial memory impairments. Conversely, we detect decreases in hippocampal theta and fast gamma power (amplitude) that progress with age in 3xTg mice and coincide with the onset of spatial memory impairments at 8-months-old. Given that hippocampal theta power is driven in part by MEC inputs, loss of hippocampal theta power may reflect further loss or dysfunction of MEC inputs. Decreased fast gamma power may indicate a combination of altered inputs and local hippocampal changes. Ongoing analysis will examine how physiological changes on the single cell level could mediate these differences. Conclusions and Future Directions: Our data highlight early desynchronization between MEC and hippocampus prior to memory impairments. This could serve as a potential early biomarker, which is notable as the importance of early detection and treatment for AD is gaining attention. We also find changes in hippocampal oscillations that progress with age and coincide with cognitive impairment. Overall, these data will inform future experiments where we manipulate these circuits to prevent or reverse memory impairments.

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Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 5R01AG067258-02
1F30AG082448-01

Title: Entorhinal cortex circuit dysfunction in mouse models of APOE4 and chemotherapy-induced cognitive impairment

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Abstract: *APOE4* has broad effects, one of which is worsened cognitive outcomes in cancer survivors following chemotherapy treatment compared to *APOE3*. We used 1-2 month old female *APOE3* and *APOE4*-Targeted Replacement (TR) mice treated with and without doxorubicin (a breast cancer chemotherapeutic) to determine 1) the effects of *APOE* genotype on normal circuit function in the entorhinal cortex- a critical brain region responsible for information gating between the cortex and hippocampus - and 2) the *APOE* genotype effects on entorhinal circuit function in the presence of doxorubicin. Whole cell patch-clamp experiments were performed in layer II/III pyramidal cells in the entorhinal cortex and cells were filled with 0.5% biocytin to visualize morphology *post hoc* under a confocal microscope. Two types of excitatory cells were identified based on morphology: pyramidal and stellate. Chemotherapy was introduced via a single intraperitoneal injection of doxorubicin (10 mg/kg) or saline (control). Mice were euthanized one-week post-injection. We found that pyramidal cells in the entorhinal cortex of *APOE4*-TR mice (4 mice, n=23 cells) exhibit significantly decreased spontaneous inhibitory postsynaptic current frequencies, thereby contributing to an elevated excitatory-inhibitory balance compared to *APOE3*-TR mice (4 mice, n=22 cells). Doxorubicin-treated *APOE3*-TR mice (4 mice, n=28 cells) showed a significant increase in spontaneous excitatory and inhibitory postsynaptic current amplitude compared to controls (2 mice, n=13 cells), while doxorubicin-treated *APOE4*-TR mice (5 mice, n=18 cells) displayed no such synaptic changes compared to controls (4 mice, n=18 cells). These findings suggest that 1) *APOE4* brains have baseline deficits in entorhinal cortex circuit inhibition and 2) *APOE4* brains lack a robust response to chemotherapy, potentially increasing vulnerability to cognitive impairment. To investigate inhibitory-specific dysfunction in the entorhinal cortex, we bred *APOE* mice with TdTomato/Parvalbumin (PV)-Cre mice to look at passive and active properties of PV cells - the most abundant inhibitory cell type in the entorhinal cortex.

Disclosures: **N. Luo:** None. **S. Vicini:** None. **G. Rebeck:** None.

Poster

PSTR256. Alzheimer's Disease: Neural Circuits

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Title: Intrinsic neural timescales link structural and network abnormalities in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is associated with brain atrophy and atypical functional changes in the default mode network (DMN). However, much remains unknown regarding the brain region(s) whose local brain atrophy induces atypical network activity in the DMN. We measured intrinsic neural timescales (INT) to potentially identify one or more brain regions that trigger such DMN abnormalities and to bridge knowledge gaps between atypical structural and functional changes in the DMN in AD. INT, known as temporal receptive windows or temporal receptive fields, represents the time window for one brain region to integrate inputs from other regions. The DMN, which receives inputs from myriad brain areas, has a crucial role in cognitive capability in older adults (Ezaki et al., 2018) and typically exhibits longer INT compared to other sensory-related brain regions. Furthermore, a previous study that focused on autism spectrum disorder revealed that atypically shorter INT in the sensory cortex was a key mediating factor to account for a significant correlation between the atypical reduction in the grey matter volume (GMV) in the regions and autistic symptoms (Watanabe et al., 2021). These outcomes suggest that INT may link local neuroanatomical changes to atypical neural processes and lead to DMN impairment and cognitive symptoms of AD. Here, we compared INT, using resting-state functional MRI methods, between patients diagnosed with AD and age-/sex-/handedness-matched cognitively healthy individuals. We first performed an exploratory whole-brain analysis and found a shorter INT only in the left angular gyrus (AG) in the AD group compared to the cognitively normal group. We also found that the left AG exhibited AD-specific decreases in

GMV and that the diminished GMV induced the shorter INT in the left AG, which in turn caused shortened overall INT within the DMN. In addition, we found that the overall INT of the DMN was associated with the symptomatic severity of AD, especially for attention-related functions. Taken together, the left AG represents a crucial region whose structural atrophy and resultantly shorter INT leads to DMN impairment, which consequently results in AD symptoms. Given that INT length indicates the capacity of local information integration, these findings suggest that, in individuals with AD, the atrophy of the left AG disturbs the DMN's capability to integrate information from diverse neural inputs, which underlies a part of cognitive decline in AD. Our findings suggest the possibility that INT of the left AG could serve as a convenient biomarker for diagnostic and therapeutic use.

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Poster

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Title: Differential neural circuit vulnerability to β-amyloid and tau pathologies in Alzheimer's disease mice

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Abstract: Alzheimer's disease (AD) is characterized by memory loss and neuropsychiatric symptoms, but how amyloid-β (Aβ) and microtubule-associated protein tau (*MAPT*) cooperate to cause synaptic changes underlying memory and emotional disturbances in dementia is largely unknown. We employed pathological, behavioral, tissue clearing/expansion microscopy, and bulk and cell-specific transcriptomic approaches to evaluate sex and aging effects of amyloid-β (Aβ) and/or tau pathologies on memory- and emotional-related neural circuits in amyloid precursor protein (APP), Tau and double APP/Tau transgenic mice. Compared to single transgenic mice, Aβ pathology increased phosphorylated tau in the hippocampus of 9 month-old

APP/Tau mouse females, whereas tau had not effect on amyloid pathology, indicating that Aβ promotes tau pathology. Interestingly, APP/Tau mice develop learning and memory deficits associated with tau pathology in hippocampal excitatory neurons, whereas innate anxiety and impaired fear memory extinction were linked to Aβ accumulation in the basolateral amygdala (BLA). Tissue clearing/3D imaging in novel neuronal activity reporter AD mice (APP/Tau;*c-fos*$_{p}$-EGFP) revealed impaired activation of excitatory neurons coinciding with synaptic accumulation of tau and reduced synaptic proteins in the hippocampus. Importantly, transcriptional profiling reveals region-specific but also common transcriptional changes in response to Aβ/tau pathology in the hippocampus and BLA, including deregulation of 63 AD risk genes involved in synapse transmission and inflammation. These findings indicate that APP/Tau mice reproduce pathological, behavioral, synaptic, and transcriptional changes linked to known molecular determinants of AD development. The differential regional effects of Aβ and tau in emotional- and memory-related neural circuits provide evidence that both factors should be considered in future AD therapeutic strategies.

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Poster

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Program #/Poster #: PSTR256.23/E1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Masupirdine (SUVN-502), a pure 5-HT$_6$ receptor antagonist: Rationale for evaluation in patients with agitation in dementia of Alzheimer's type

Authors: *P. JAYARAJAN, R. MEDAPATI, V. GRANDHI, R. ABRAHAM, R. BADANGE, K. BOJJA, S. MANCHINEELLA, A. SHINDE, R. NIROGI;
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Abstract: Agitation in Alzheimer’s disease (AD) is one of the disabling neuropsychiatric symptoms most commonly observed in AD. It affects the patients’ quality of life and results in considerable caregiver distress. Currently there are limited pharmacological agents for the management of agitation. The commonly used agents possess modest efficacy and carry several notable safety concerns like increased risk of mortality, sedation, falls, and worsening of cognitive skills. Thus, there is a need for novel, efficacious and safe agents. Serotonin-6 (5-HT$_6$) receptors are G-protein-coupled receptors with unique localization and specific distribution in the brain regions having a role in mood, and behaviour. In addition, clinically used psychotropic agents have strong affinity for 5-HT$_6$ receptors. Thus, modulation of 5-HT$_6$ receptors may have therapeutic utility for behavioural disorders. Masupirdine is a pure and potent 5-HT$_6$ receptor antagonist. In animal models for aggressive behaviour i.e., dominant-submissive assay (DSA) and resident-intruder task (RIT), masupirdine was evaluated at doses ranging from 1 to 10

mg/kg. Oral administration of masupirdine significantly ($p<0.05$) attenuated aggressive behaviors. In addition, masupirdine significantly modulated levels of dopamine and norepinephrine in brain at a dose of 10 mg/kg, *s.c.* The post hoc analysis of the Phase-2 study (NCT02580305) in patients with moderate AD suggested treatment with masupirdine at 50 mg and 100 mg significantly decreased the agitation/aggression score from Week 13 to Week 26 suggesting potential treatment effects of masupirdine on agitation/aggression symptoms. To explore the beneficial effects, masupirdine is currently being evaluated as a monotherapy in a global Phase-3 study for the potential treatment of agitation in participants with dementia of Alzheimer's type (NCT05397639).

Disclosures: **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Grandhi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Badange:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Bojja:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Manchineella:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shinde:** 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

PSTR256. Alzheimer's Disease: Neural Circuits

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Program #/Poster #: PSTR256.24/E2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: EXC 2145 SyNergy

Title: The impact of locus coeruleus vulnerability in early manifestations of Alzheimer's disease

Authors: *C. KLAUS[1,2], K. OCHS[1], F. STRÜBING[1,3], P. FEYEN[1], J. GENTZ[1], G. BIECHELE[4], M. SCHWEIGER[5], R. PERNECZKY[5,1,2,6], M. SCHMIDT[3], B. RAUCHMANN[4], M. BRENDEL[4,2], L. PAEGER[1], J. HERMS[1,2,3];
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Abstract: Background. The locus coeruleus (LC), the main noradrenergic nucleus and primary source of noradrenaline (NA) in the forebrain is one of the earliest brain regions affected in Alzheimer's disease (AD). Patients with AD often experience olfactory deficits decades before the onset of cognitive impairments, highlighting the potential of early diagnosis for effective

treatment. Here, we seek to better understand the mechanisms underlying the vulnerability of the LC in the context of olfaction. **Methods.** We used female and male wild-type (WT, C57BL/6J) mice and transgenic APP^{NL-G-F} mice, aged between 1 and 12 months. **Results.** Our immunohistochemical findings reveal an age-dependent loss of LC-noradrenergic axons in the olfactory bulb (OB), starting as early as 2 months. Notably, at 3 months of age, LC axonal loss is exclusively observed in the OB. This loss coincides with olfactory dysfunction, as demonstrated by impaired performance in a buried food test. Reducing NA release in the OB by optogenetics recapitulates the olfactory phenotype. We observe altered electrophysiological properties of LC neurons in 6-month-old APP^{NL-G-F} mice compared to WT mice. Importantly, the integrity of mitral cells, the main output neurons in the OB, remains unaffected. Asking for the underlying mechanism of LC axon loss we hypothesized that microglia engulf damaged LC axons. To test this, we investigated the role of the translocator protein (TSPO) in LC vulnerability. The LC axon loss is reduced in APP^{NL-G-F} crossed with TSPO-KO mice and the olfactory performance remains unaltered compared to WT animals. This suggests that microglia, the main cell type expressing TSPO, are involved in the degradation process of LC axons. We also conducted positron emission tomography (PET) scans to assess early neuroinflammation and show elevated TSPO-PET signals in the OB region of patients with mild cognitive impairment, which did not further increase in AD patients. All patient groups show hyposmia and the post-mortem tissue analysis of a different cohort of prodromal AD patients reveals a decline of LC axons in the OB. **Discussion.** In summary, our study highlights the early-onset loss of LC-noradrenergic axons in the OB and its contribution to olfactory dysfunction in a mouse model of AD and in post-mortem brain tissue from prodromal AD patients. Additionally, we provide evidence suggesting the involvement of microglia in the LC-axon vulnerability. Our findings elucidate the early changes in the LC and offer insights into the potential mechanisms underlying olfactory deficits in AD, thereby providing a potential target for therapeutic strategies aiming at slowing or halting the disease progression.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

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Program #/Poster #: PSTR256.25/E3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG062581
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Title: Consequences of locus coeruleus degeneration in a rat model of Alzheimer's disease

Authors: *A. E. MARRIOTT[1], M. A. KELBERMAN[1], A. KORUKONDA[1], J. P. SCHROEDER[2], K. E. MCCANN[1], D. WEINSHENKER[1];
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Abstract: Background: The noradrenergic locus coeruleus (LC) is exceptionally susceptible to insult during Alzheimer's disease (AD), beginning with the early accumulation of hyperphosphorylated tau and culminating in frank neuronal loss. Inducing LC damage with the selective neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride (DSP-4) exacerbates AD-like neuropathology and cognitive impairment in amyloid-based murine models of AD, indicating a causal relationship between LC degeneration and disease progression. Unlike other rodent models, TgF344-AD rats display both amyloid and tau pathology and develop endogenous tau in the LC prior to other brain regions, as observed in human AD. By inducing LC-specific damage in TgF344-AD rats using DSP-4, this study will explore the impact of LC degeneration on AD- and noradrenergic-relevant behaviors.
Methods: At ~1 month of age, male and female TgF344-AD rats and wild-type littermates received 2 doses of DSP-4 (50 mg/kg) or saline spaced 1 week apart, followed by single monthly injections until ~5 months of age. Behavioral testing began ~1 week following the final injection to assess changes in social behavior, stress-induced repetitive behaviors, arousal, anxiety-like behavior, and learning and memory.
Results: The effects of DSP-4 were more pronounced than those of genotype. In general, DSP-4 treated animals showed blunted stress-induced repetitive behaviors and circadian locomotor activity. DSP-4 animals also displayed augmented contextual freezing in a fear conditioning paradigm.
Conclusions: We have shown that depletion of NE by DSP-4 has profound effects of stress-induced repetitive behaviors, locomotor activity, and contextual fear memory. The reduction in repetitive behaviors such as nestlet shredding and stick chewing, as well as diminished locomotor activity in NE-depleted rats is consistent with the important role of LC-NE transmission in arousal.
Typically, 7-8-month-old TgF344-AD rats do not display deficits in fear conditioning, a measure of associative learning. Because LC degeneration is correlated with cognitive deficits in human AD, we expected LC lesions would unmask this phenotype, causing DSP-4 treated animals to exhibit less contextual freezing. However, the opposite effect was observed.
The next step is to assess the effects of the DSP-4 on AD-like pathology and noradrenergic dysfunction in the TgF344-AD rats using immunohistochemistry and high-performance liquid chromatography. Based on previous experiments in other rodent models of AD, it is anticipated that neuroinflammation, Aβ, and aberrant tau will be exacerbated in DSP-4 treated TgF344-AD rats.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG076239

Title: Disrupted neuromodulatory regulation of cortical network dynamics in Alzheimer's Disease

Authors: *P. XU, C. BARNES, R. OREN, S. COOK, J. NWAINOKPOR, J. A. CARDIN; Yale Univ., New Haven, CT

Abstract: Disruption of major neuromodulatory centers, including the cholinergic neurons of the basal forebrain Nucleus Basalis (NB), is a hallmark of multiple neurodegenerative diseases such as Alzheimer's Disease (AD). Loss of coordinated cholinergic signaling likely contributes to perturbation of state-dependent neural activity and cognitive functions, including attention, arousal, and memory. Both cellular degeneration of the basal forebrain and the cognitive impacts of decreased cholinergic signaling are recapitulated at older ages in mouse models of AD, suggesting that early detection of neuromodulatory dysregulation could be a key biomarker of initial pathology. We recently developed an approach for dual-color mesoscopic imaging of neuromodulatory release and neural activity across the dorsal cortex of awake behaving mice. Because imaging can be performed through the skull and requires only short sessions, animals can be imaged across the lifetime in a moderate-throughput screen. Using this approach, we imaged cholinergic release and neural activity in animals from the APP/PS1 and AppNL-G-F/MAPT dKI mouse lines across ages. To express genetically encoded indicators for acetylcholine (ACh) and calcium, we injected AAVs carrying ACh3.0 and RCaMP1b into the transverse sinus of neonatal mice from both lines and wildtype controls. Behavioral states were continuously monitored using pupillometry, running speed, and facial motion. Regression analyses were used to examine the predictive relationship between ACh and calcium signaling in different cortical regions across behavioral states. In young adult mutants and controls, both ACh and calcium activity exhibited significant spatial and temporal heterogeneity, varying with behavioral state and cortical region. Correlation analyses revealed state-dependent differences in the spatial structure of cholinergic signaling and the coupling between ACh signaling and local cortical activity, which varied reliably across cortical areas and behavioral states. At later time points (>P240), we observed a progressive disruption of state-dependent cholinergic signaling in mutants from both lines. Mutant mice showed a loss of the correlational structure for both ACh and calcium signals across cortical areas, which became more pronounced with increasing age. Additionally, AD mutants in both groups exhibited a decoupling between cholinergic and local cortical activity. Together, our results suggest a progressive disruption of cholinergic signaling in AD mutants that culminates in a loss of state-dependent regulation of neuronal activity and a loss of spatiotemporal coordination of network activity.

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Poster

PSTR256. Alzheimer's Disease: Neural Circuits

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Dopaminergic neuron degeneration and loss of reward processing in an Alzheimer's disease rat model

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Abstract: Alzheimer's disease (AD) is typically characterized by memory loss and the accumulation of neuropathological markers, however neuropsychiatric symptoms of AD, such as apathy, are often overlooked. Degeneration of dopaminergic neurons in the ventral tegmental area (VTA) have been implicated in the loss of motivated behaviors in both an AD mouse model and human patients. Using a transgenic AD rat model expressing both behavioral phenotypes and histological markers consistent with the AD human population (TgF344-AD “AD rats”), we investigated motivated behavior to a natural reward. We conducted a conditioned place preference (CPP) in which one side was paired with Froot Loops as the palatable reward and the other side was paired with food chow (6 pairings each, 1 pairing/day) in AD and wild-type (WT) littermate control rats of both sexes at ages 2-3 months (WT, n=6, AD n=7) and 6-7 months (WT, n=12, AD n=12) of age. We found that 2-3-month rats formed a conditioned place preference to the chamber paired with the palatable reward, but this preference was absent in 6-7-month-old AD rats (Δpreference, AD=-0.04 +/- 0.07, WT= 0.29 +/- 0.08, $t=3.1$, $p<0.01$). In addition, we found a decrease in consummatory behavior of the palatable reward relative to the food chow in AD rats relative to WT rats at 6-7-months but not at 2-3 months (reward type x age x genotype interaction: $F=23.5$, $p<0.0001$) suggesting that age-related deficits in conditioned place preference in AD rats could be due to an age-dependent decrease in the motivational value of Froot Loops to AD rats. This loss of CPP could also indicate a contextual learning deficit, thus, we performed a conditioned place aversion assay in which we paired one side of the conditioned place chamber with raucous sounds and flashing lights and the other paired with no noise in AD (n=12) and WT (n=16) rats. We found that at 6-7 months of age, both AD and WT rats form a conditioned place avoidance (Δpreference, WT: -0.34 +/- 0.07, AD: -0.32 +/- 0.1, $t=0.1$, $p=0.91$). Together, these findings suggest that the inability of the AD rats to form a preference to the context predicting the palatable reward is likely not due to impairment in contextual learning at this age. Finally, in our 6-7-month-old AD rats, we also found a significant loss of Tyrosine Hydroxylase (TH+) cells in the VTA, potentially indicating that the inability to form a preference may be linked with a loss of dopamine. Together, these findings indicate an age-dependent decrease in motivation in AD rats for a palatable reward that is not due to deficits in contextual memory.

Disclosures: **B.E. Linneman:** None. **L.A. Adrian:** None. **T.J. Sloand:** None. **M. Niedringhaus:** None. **E.A. West:** None.

Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.28/E6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1AG069378
NIH RF1AG072727
NIH R01AG048993

Title: Examining noradrenergic changes in the AppNL-G-F mouse model of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD)-associated neuronal death has been hypothesized to include degeneration of the norepinephrine (NE) producing locus coeruleus (LC) neurons as an initial region of loss responsible for propagating death to efferent projection areas. However, the mechanisms explaining this early and preferential dysfunction of the noradrenergic system remain unclear. To better understand LC changes during disease we compared littermate control six-month-old male and female C57BL/6 wild type mice to the *App*$^{NL-G-F}$ knock-in model of AD (n=6). Immunostaining for tyrosine hydroxylase, as the rate-limiting enzyme for norepinephrine synthesis, was used to quantify cell loss in the LC. As a relevant efferent output of the LC, we quantified norepinephrine levels in the hippocampus and compared this, via western blot, to levels of the catabolic enzymes, monoamine oxidase A (MAO-A), catechol O-methyltransferase (COMT), and monoamine oxidase B (MAO-B). Western blot analysis was also used to assess overall presynaptic and post-synaptic compartment integrity through quantifying levels of synaptophysin and PSD95, respectively. Finally, compensatory changes in noradrenergic receptor levels were also quantified by western blot. As expected, we observed a significant reduction in hippocampal NE levels in both male and female *App*$^{NL-G-F}$ mice. Surprisingly, this did not correlate with any change in TH immunoreactivity in the LC suggesting that cell death was not responsible for the observed decrease in NE. To investigate whether the decrease in NE levels might result from altered norepinephrine turnover, we assessed levels of COMT, MAO-A, and MOA-B and observed a selective increase in MAO-A levels in both sexes of *App*$^{NL-G-F}$ mice compared to wild type controls. As a possible consequence of the NE deficiency, we quantified a decrease in hippocampal protein levels of beta-2 adrenergic receptors (β2-AR) in male and female *App*$^{NL-G-F}$ mice compared to wild-type controls. There were no differences in synaptophysin or PSD95 in *App*$^{NL-G-F}$ compared to wild type mice in either sex suggesting no overall synaptic loss in the hippocampus. Our findings revealed a specific modulation of β2-AR

and MAO-A levels in the *App*$^{NL-G-F}$ mice that is not associated with robust cell death or synaptic loss. These data suggest a potential selective disruption in adrenergic signaling. Moreover, this change in NE neuron function may identify an early phenotype change during disease that precedes or contributes to eventual neuron and synaptic loss.

Disclosures: **N. Kilic:** None. **H. Kaur:** None. **C. Combs:** None.

Poster

PSTR256. Alzheimer's Disease: Neural Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR256.29/E7

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant U24AG072701
R01MH127737

Title: Genetic and social influences on cognitive flexibility and fronto-insular circuits in a mouse model of Alzheimer's Disease

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Abstract: Social interaction is an important factor in the progression of Alzheimer's Disease (AD), a dementia that impairs an individual's cognitive functions. Recent research has implicated the fronto-insular cortical circuits in socioemotional processing and regulation of cognitive flexibility. However, how social interaction influences AD pathology in fronto-insular cortices and cognitive flexibility associated with these regions is unknown. Here, using the APP/PS1 mouse model of amyloidosis, we investigated how APP/PS1 mutations and social housing impact fronto-insular pathology and cognitive flexibility in the attentional set-shifting task (AST). Three-month-old adult APP/PS1 and wild-type (WT) mice were housed in group or isolation for one month and then tested in AST, followed by histological assays of AD-related biomarkers. Our data showed that these four groups of mice performed similarly well in simple sensory discrimination tasks to obtain food reward, suggesting intact sensorimotor and motivation functions in the early stage of this APP/PS1 model. In contrast, APP/PS1 mice exhibited significant deficits in shifting attention to relevant cues in a different sensory dimension, which is known to depend on fronto-insular function. Furthermore, APP/PS1 mice showed greater individual variations in cognitive performance compared to WT mice, and these variations were moderated by social housing and body weight loss due to food restriction before AST. Interestingly, group housed APP/PS1 mice with more weight loss exhibited greater cognitive impairment relative to APP/PS1 mice with less weight loss, or WT mice of comparable weight loss, whereas an opposite trend was observed in isolated mice. Additional histological analyses revealed increased amyloidosis and microglia coverage, as well as altered c-Fos gene

expression, in prelimbic and anterior insular cortices of socially isolated mice compared to group housed mice. Together, these results indicate that fronto-insular dependent cognitive flexibility function is particularly vulnerable to the detrimental effects of APP/PS1 mutations. Our studies further suggest that social interaction and bodily changes jointly moderate the severity of cognitive impairment in individual animals with genetic dispositions to AD, which may provide a model system to investigate the underlying neural mechanisms and test potential intervention strategies.

Disclosures: **H. Wnuk:** None. **Y. Zuo:** None. **K. Wang:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.01/E8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA RF1 Grant AG056114
Training Grant T32MH073526

Title: BAC transgenic mouse model of human MS4A4E modifies amyloid pathology and transcriptome in 5xFAD mice

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Abstract: Genome Wide Association Studies (GWAS) have identified several AD risk loci in the Membrane-Spanning 4-Domains subfamily A (MS4A) gene cluster on chromosome 11. The MS4A genes are expressed in myeloid cells, including microglia, and are involved in immune response and regulation. One of the most significant traits associated with these MS4A variants is the level of soluble Triggering Receptor Expressed on Myeloid Cells 2 (sTREM2), a biomarker of AD, in the cerebrospinal fluid. However, it is unknown how these MS4A genes confer risk and how they are connected to sTREM2 processing and secretion. We generated a Bacterial Artificial Chromosome (BAC) transgenic mouse model to express the MS4A gene cluster (named BAC-MS4A mice). The BAC contains a human genomic locus, encompassing MS4A4A, MS4A6A, MS4A4E, and their surrounding proximal regulatory region. Notably, the mice carrying MS4A BAC only express human MS4A4E, a gene that has yet to be understood in the context of AD pathogenesis, but not MS4A4A or MS4A6A. We crossed BAC-MS4A mice with 5xFAD, an amyloid depositing mouse model of AD, and found an exacerbation of plaque pathology in male, but not female, 5xFAD/BAC-MS4A mice in both the cortex and hippocampus at 7 months old. The plaques in the cortex and hippocampus of 5xFAD/BAC-MS4A males were also more fibrillary than those of 5xFAD control mice. Moreover, RNA sequencing analysis of cortical tissue also revealed a sex-dependent increase in the number of

differentially expressed (DE) genes in male 5xFAD/BAC-MS4A compared to 5xFAD controls, including further upregulating the expression of several Disease-Associated Microglia (DAM) genes. Together, our results indicate that human-specific MS4A4E could be a modifier of amyloid AD. This human genetic mouse model could be used to decipher the role of the MS4A gene locus in AD pathogenesis, and the mechanism underlying the association between sTREM2 and the MS4A gene cluster.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.02/E9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Key R&D Program of China (2021YFE0203000)
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Chow Tai Fook Charity Foundation (CTFCF18SC01)

Title: Integration of polygenic risk and protein biomarkers using deep learning methods for Alzheimer’s disease prediction

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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disease with complex etiology. Predicting AD risk is critical for early diagnosis and disease intervention. AD is attributed to polygenic genetic components; multiple variants across the human genome thus jointly contribute to disease susceptibility. The polygenic nature of AD allows life-time risk prediction by evaluating polygenic risk scores (PRSs) accounting for the combined effects of disease-associated genetic variants. Meanwhile, many AD biomarkers have been developed to examine disease risk and progression, such as plasma amyloid beta, phosphorylated tau, and neurofilament light proteins. Given the complexity of AD etiology, nonlinear interactions among genetic variants and the crosstalk between genetic and non-genetic factors play critical roles in the modulation of disease risk, while traditional (generalized) linear models fail to consider such effects. Nonetheless, deep learning methods can capture nonlinearity within high-dimensional data, which may enable more accurate disease risk prediction and improve our understanding of AD etiology. Accordingly, we developed a neural network model to model the nonlinear polygenic risk and its interaction with protein biomarkers for predicting AD. Our comprehensive analyses demonstrate that the neural network model outperforms the traditional regression models for predicting AD risk. Moreover, we stratified the genetic risks by performing unsupervised clustering based on the polygenic risk and plasma protein biomarkers. We showed that the stratified disease risks correlate with critical disease-associated biological pathways. Therefore, our findings suggest that deep learning methods are effective in leveraging multi-omic profiles for predicting and stratifying AD risk.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant U54 AG054349
NINDS Grant R01NS083801

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NIA Grant RF1AG065329

Title: The Abca7V1613M variant confers protective phenotypes in the 5xFAD mouse model

Authors: *C. A. BUTLER[1], A. MENDOZA ARVILLA[1], G. MILINKEVICIUTE[1], C. DA CUNHA[1], S. KAWAUCHI[2], A. THACH[1], K. O'GARA[3], K. TRAN[1], N. REZAIE[4,5], D. JAVONILLO[1], L. A. HOUCHIN[6], J. PHAN[1], A. J. TENNER[1], F. M. LAFERLA[1], A. MORTAZAVI[4], G. R. MACGREGOR[2], K. N. GREEN[1];
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Abstract: Variants within *ABCA7*, which encodes a member of the ABC lipid transporter superfamily, can be associated with increased risk of late onset Alzheimer's disease (LOAD). Knock out studies have implicated ABCA7 in microglial phagocytosis, clearance, and lipid metabolism. The human ABCA7 variant V1599M, encoded by SNP rs117187003, has been reported to have differential risk for developing LOAD in GWAS meta-analyses. We used CRISPR to generate mice with an *Abca7^{V1613M}* allele, which models the human V1599M variant, and crossed these mice with the 5xFAD mouse model of amyloidosis. Primary microglia from *Abca7^{V1613M}* homozygous pups, in the absence of amyloid beta (Aβ) pathology, had increased phagocytic capacity for beads and Aβ1-42 peptide compared to wild-type controls, indicating the involvement of ABCA7 in microglial phagocytosis. Furthermore, differential gene expression profiles were observed between wild-type and *Abca7^{V1613M}* mice after LPS challenge, which suggested impaired resolution of inflammation in *Abca7^{V1613M}* mice.We also investigated the effects of the *Abca7^{V1613M}* variant on lipid metabolism. Analysis of plasma lipids showed increased cholesterol and trending increases in HDLs, triglycerides, and vLDLs in homozygous *Abca7^{V1613M}* mice. Bulk lipidomics of cortical tissue revealed distinct changes in lipid composition in 5xFAD hemizygous/*Abca7^{V1613M}* homozygous mice compared to 5xFAD controls, including increased phospholipids. Regarding Aβ plaque pathology, 5xFAD/*Abca7^{V1613M}* mice had fewer plaques in the cortex and subiculum compared to 5xFAD mice, which was sustained from 4 to 12 months of age. 5xFAD/*Abca7^{V1613M}* mice also showed reduced Aβ-40 and -42 in both insoluble and soluble fractions of hippocampal and cortical tissue compared to 5xFAD controls. Western blot analysis revealed reduced full-length APP and C-terminal (C99/C83) fragments, but no effect on BACE-1, PSEN1, or ADAM-10 in 5xFAD/*Abca7^{V1613M}* mice compared to 5xFAD controls. 5xFAD/*Abca7^{V1613M}* mice also had reduced Aβ-associated inflammation, as indicated by bulk RNA-seq and WGCNA analysis, and reduced microgliosis and astrogliosis. There were age-associated changes in neuronal damage, with reduced LAMP1, plasma and brain NfL levels in 5xFAD/*Abca7^{V1613M}* mice compared to 5xFAD controls in both 4- and 12-month animals.Overall, the findings suggest that the *Abca7^{V1613M}* variant influences phagocytosis, response to LPS challenge, lipid metabolism, Aβ pathology, inflammation, and neuronal damage in the 5xFAD mouse model. The variant may confer a gain of function for ABCA7 and potentially contribute to a protective effect against AD-related pathology.

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Poster

PSTR257. Alzheimer's Disease: Genetics

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01NS131620

Title: From Transcription to Degeneration: Investigating Dysregulation of R-Loop Homeostasis in Neurodegenerative Disorders

Authors: *E. M. ARNOLD[1], J. L. BURFORD[1], D. J. MORTON[1], L. A. HIGGINSON[1], N. A. BARR[1], A. SETH[2];
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Abstract: A substantial amount of effort has been devoted to investigating the dysregulation of protein homeostasis in neurodegenerative diseases. Despite this, our understanding of the underlying mechanisms responsible for initiating or perpetuating these phenotypes remains incomplete. Mounting evidence suggests that the dysregulation of transcriptional regulatory events, including the formation of regulatory DNA:RNA hybrids (R-loops), are key factors in the pathogenesis of neurodegenerative disease. R-loops are transient, mainly co-transcriptional, three-stranded structures that consist of an RNA:DNA hybrid and a single-stranded DNA strand that is displaced by the RNA strand. In addition to their role in genomic instability, R-loops are thought to contribute to gene expression by inducing changes in chromatin structure, thereby modulating lineage-specific promotor-enhancer interactions. Interestingly, mutations in key regulatory proteins required for R-loop resolution and homeostasis are associated with a variety of neurodegenerative diseases. Thus, dysregulation of R-loop homeostasis may serve as a potential unifying initiating event that underlies a spectrum of neurodegenerative disorders. The goal of this study is to identify associations between pathological R-loops, altered gene expression and neurodegenerative phenotypes. To examine R-loop homeostasis, we have begun to systematically and comparatively examining the formation and/or persistence of R-loops and their effect on gene expression by utilizing well-established Drosophila models of neurodegenerative disease (Alzheimer’s disease, Parkinson’s disease, and ALS). To begin to assess the formation of R-loops across distinct age-related neurodegenerative disorders in Drosophila, we employed S9.6 antibody-mediated slot blots utilizing fly brain tissue. Our preliminary findings indicate that we can detect R-loops in flies modeling neurodegenerative disease. Given that several recent studies that challenge the reported specificity of S9.6 antibody toward RNA:DNA hybrids, we will perform a modified CUT& RUN approach termed MapR in flies. MapR exploits the natural affinity of RNase H to detect RNA:DNA hybrids. The combination of these approaches will allow comprehensive understanding of the impact of

aberrant R-loop formation on gene expression in neurodegenerative disorders. Thus, this integrated approach will provide insights into the specific targets affected by R-loop-mediated pathological processes and underlying neurodegenerative diseases.

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Poster

PSTR257. Alzheimer's Disease: Genetics

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: University of Washington Alzheimer's Disease Research Center development project award

Title: Presense of pathogenic variants in circular RNA of presenilin 1 and 2

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Abstract: Alzheimer’s Disease (AD) is the most common form of neurodegeneration, currently affecting over 6 million Americans. Previous research suggests that circular RNAs (circRNAs) are heavily implicated in neuronal gene regulation; however, their precise role in AD pathogenesis has yet to be established. In this study, we examined circRNA of two AD-causing genes, presenilin 1 and 2 (PSEN1 and PSEN2), for the presence of pathogenic variants. cDNA from individuals with familial AD (FAD) was PCR amplified using divergent primers to target back-spliced regions specific to circRNAs, and the purified PCR product was subsequently Sanger sequenced. Four variants, I143T, S212Y, V272A in PSEN1, and N141I in PSEN2, were identified in circRNAs. The presence of pathogenic variation in circRNAs marks a crucial first step in determining their role in AD pathogenesis. To our knowledge, this research is the first of its kind to identify pathogenic variants in circRNAs of AD risk genes.

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Poster

PSTR257. Alzheimer's Disease: Genetics

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: The RELN-COLBOS mouse model of resilience to Alzheimer's disease

Authors: *C. MARINO[1], S. AREVALO-ALQUICHIRE[1], H. GORDON[1], P. PEREZ-CORREDOR[1], D. SEPULVEDA-FALLA[2], Y. T. QUIROZ[3], J. F. ARBOLEDA-VELASQUEZ[1]; [1]Dept. of Ophthalmology, Harvard Med. Sch., Boston, MA; [2]Inst. für Neuropathologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [3]Massachusetts Gen. Hosp., Boston, MA

Abstract: We recently characterized the second patient with extreme protection against autosomal dominant Alzheimer's disease (ADAD) caused by the Presenilin-1 (PSEN1) E280A mutation. This male individual did not develop mild cognitive impairment until his 70s, more than two decades after the expected age at onset for his family. We discovered that his resilience against ADAD was facilitated by the presence of a rare mutation in the RELN gene, the H3447R (termed RELN-COLBOS mutation). The gain of function of RELN-COLBOS, along with our previously discovered loss of function of ApoE3 Christchurch variant, allowed us to hypothesize the presence of a converging mechanism of protection against ADAD characterized by the reduced interaction of ApoE and the increased interaction of RELN with heparan sulfate proteoglycans (HSPGs). Here, we characterized the function of RELN-COLBOS mutation by generating a novel knock-in transgenic mouse model, using neuronal density analysis, immunohistochemistry, western blotting, and behavioral studies. Our data confirmed that the RELN-COLBOS mutation is sexually dimorphic and operates via increased phosphorylated disabled-1 protein (pDAB1) levels, and reduced tau hyperphosphorylation. The RELN-COLBOS mutation also improved motor functions in a crossed mouse model to a transgenic tau model, thus validating its protective effect and suggesting therapeutic potential against dementia.

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drug study, report that research relationship even if those funds come to an institution.; R01 AG054671, AARGD-591030, RF1AG077627. **J.F. Arboleda-Velasquez:** 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.; Open Philantrophy, Good Ventures, UH3 NS100121, RF1 NS110048.

Poster

PSTR257. Alzheimer's Disease: Genetics

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Program #/Poster #: PSTR257.07/E13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant GM145364
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Title: Increased ER-to-mitochondria calcium signaling due to presenilin loss results in lysosomal enlargement and alkalization

Authors: K. C. RYAN, Z. ASHKAVAND, J. T. LABOY, *K. R. NORMAN;
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Abstract: Compromised lysosome function is implicated in the pathology of many neurodegenerative diseases. Alzheimer’s disease (AD) models show defective clearance of lysosomal contents, but the cause is unclear. Familial Alzheimer’s disease (FAD) is caused primarily by mutations in the presenilin encoding genes, but the underlying mechanism remains obscure. We previously reported that loss of the conserved *C. elegans* presenilin orthologue SEL-12 results in increased mitochondrial calcium, which promotes mitochondrial dysfunction and neurodegeneration. Here, we find that the lysosomes in *sel-12* null mutants are significantly enlarged and more alkaline due to increased ER-to-mitochondrial calcium signaling. We further show that lysosome dysfunction is independent of SEL-12 protease function. Additionally, these defects and their dependence on mitochondrial calcium are recapitulated in human FAD cells, demonstrating a conserved role for mitochondrial calcium in presenilin-mediated lysosome dysfunction. We also find that *sel-12* mutants have increased contact surface area between the ER, mitochondria, and lysosomes, suggesting *sel-12* has an additional role in modulating organelle contacts and organelle communication. Overall, we have demonstrated that SEL-12 maintains lysosome acidity and lysosome health by controlling ER-to-mitochondrial calcium signaling.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.08/E14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA grant RF1 AG074566
Paul & Carol Stark Fellowship

Title: Total PLCG2 ablation impairs microglial responses and confers diverse transcriptional alterations in a murine model of Alzheimer's disease

Authors: *E. J. MESSENGER[1], A. P.-Y. TSAI[4], P. B.-C. LIN[5], G. XU[1], A. N. ANSARI[1], A. OBLAK[6], B. T. LAMB[6], G. E. LANDRETH[2], S. J. BISSEL[3];
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Abstract: Many of the genes associated with altered risk for Alzheimer's disease (AD) are predominantly expressed in microglia and affect innate immune responses. Among these genes is phospholipase C gamma 2 (PLCG2), a critical mediator of transmembrane signaling that acts downstream of many immune receptors on microglia, including TREM2. PLCG2 is robustly induced by amyloid pathology in AD and recent transcriptomic studies suggest a vital role for PLCG2 in the immune response to AD pathology, learning, and metabolism. Reduction in PLCG2 activity is associated with exacerbated AD pathology, but the mechanisms underlying these effects remain unclear. Therefore, we explored the impact of *Plcg2* ablation or haploinsufficiency on amyloid pathology and microglial response in the amyloidogenic 5xFAD murine model of AD and compared this to 5xFAD mice deficient in *Trem2* to establish contributions of upstream signaling. While *Plcg2* haploinsufficiency increased X34+ and 6E10+ amyloid plaque pathology, loss of *Plcg2* in 5xFAD mice results in similar plaque burden as wildtype and *Trem2*-deficient mice. Additionally, *Plcg2* deficiency significantly impaired microglial interactions with plaques and showed reduced immunoreactivity of microglia activation marker CD68 when compared to *Plcg2*$^{+/-}$ mice. Transcriptomic analysis revealed several biological processes altered by loss of *Plcg2*, including pathways associated with the microglial response, metabolism, synapses, and cell signaling. Weighted gene correlation network analysis (WGCNA) produced many significant modules of co-expressed genes such as those associated with immunity, metabolism, mitochondrial respiration, and synaptic connectivity. Importantly, one module was differentially expressed between each genotype and contained many immune-related genes, including disease-associated microglia (DAM) genes. These findings suggest PLCG2 depletion impairs the ability of microglia to effectively transduce surface receptor signals in response to amyloid plaques, leading to a stunted immune response. Overall, this study highlights the importance of PLCG2 in the innate immune response to amyloid pathology and reveals several novel pathways which may be regulated by PLCG2.

Disclosures: **E.J. Messenger:** None. **A.P. Tsai:** None. **P.B. Lin:** None. **G. Xu:** None. **A.N. Ansari:** None. **A. Oblak:** None. **B.T. Lamb:** None. **G.E. Landreth:** None. **S.J. Bissel:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.09/E15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01NS095799

Title: Tip60 HAT-specific activators as an epigenetics-based therapeutic strategy for Alzheimer's Disease

Authors: *A. ZAYA[1], A. BHATNAGAR[1], S. KORTAGERE[2], F. ELEFANT[1];
[1]Biol., Drexel Univ., Philadelphia, PA; [2]Drexel Univ. Col. of Med., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Reduced histone acetylation in the brain caused by disruption of histone acetylation homeostasis is an early event in Alzheimer's Disease (AD) etiology that causes cognitive impairment prior to amyloid beta plaque formation. While genetics plays a role in the development of AD, over 90% of patients hospitalized for AD are diagnosed with sporadic AD, highlighting the importance of epigenetic dysregulation in disease progression. Numerous small molecules, including epigenetic modulators, are currently in clinical trials for AD. These epigenetics-based treatments aim to restore histone acetylation homeostasis by inhibiting histone deacetylases (HDACs), which remove acetyl marks from histones causing chromatin to condense, leading to a reduction in gene expression. While promising, many HDAC inhibiting treatments are not specific to one HDAC, causing side effects likely due to global hyperacetylation. Our work focuses on Tip60 histone acetyltransferase (HAT), which generates pattern-specific acetyl marks onto histones to decondense chromatin, leading to enhanced transcription. We have shown that genetically increasing Tip60 HAT levels functionally rescues both cognitive deficits and expression of critical neuroplasticity genes repressed in a well-characterized *Drosophila* amyloid precursor protein (APP) model of AD by restoring histone acetylation homeostasis. Since our findings support a neuroprotective role for Tip60 HAT in AD, we propose an epigenetics-based therapeutic strategy using small molecules that selectively activate Tip60 HAT to restore histone acetylation homeostasis. We developed small molecule compounds using a structure-based approach with a general HAT activator, then further optimized the compounds using a pharmacophore function-based approach. Using an *in vitro* HAT assay, we identified three of the compounds as robust and specific Tip60 HAT activators. Future work will elucidate the efficacy of these compounds in functional assays to assess locomotion and learning & memory in the *Drosophila* AD model and assess expression profiles of neuroplasticity genes responsible for cognitive function using real-time quantitative polymerase chain reaction (RT-qPCR). Our therapeutic strategy of designing a specific Tip60

HAT activator that restores histone acetylation homeostasis is a promising AD treatment that could address cognitive impairment that precedes other disease characteristics observed at later stages.

Disclosures: **A. Zaya:** None. **A. Bhatnagar:** None. **S. Kortagere:** None. **F. Elefant:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.10/E16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Orville Edward Egbert M.D Endowment fund
NIGMS 1R16GM145548-01

Title: Functional contribution of Scully and its interacting molecules to dementia

Authors: *C. CHEPKOSGEI[1], M. SOLIS[2], P. SABANDAL[2], K.-A. HAN[2];
[2]Biol., [1]The Univ. of Texas at El Paso, El Paso, TX

Abstract: Alzheimer’s disease and related dementias (ADRD) are neurodegenerative diseases characterized by progressive deterioration of cognitive functions. Many genetic and non-genetic (e.g., age, sleep homeostasis and social stress) risk factors are associated with ADRD. However, how these risk factors interact for ADRD remains unclear. Through an unbiased genetic screen for novel ADRD genes, we identified Scully (Scu) as a genetic risk factor interacting with social stress for dementia. Scu is a multifunctional mitochondrial enzyme and is known to bind beta amyloid peptides. The heterozygous *Scu* flies (*Scu/+*) exhibited accelerated loss of memory and inhibitory control. To identify the cellular pathway by which Scu mutation causes dementia, we investigated the molecules known to interact with Scu (SIMs for Scu interacting molecules) physically or genetically. We generated the flies transheterozygous for Scu and individual SIMs (56 out of total 59 SIMs) and assessed their inhibitory control capacities at the ages of 4 days, 2 weeks, and 4 weeks. At 4-days old, all *Scu/SIM* double heterozygous lines showed normal inhibitory control. At 2 and 4 weeks old, however, 9 double heterozygous lines exhibited dysfunctional inhibitory control. This suggests that the positive hit SIMs function in the Scu signaling pathway for dementia. We are currently investigating the cellular and neural mechanisms by which SIMs interact with Scu for dysfunctional inhibitory control. The findings of our study will narrow the knowledge gap on the cellular pathways leading to ADRD.

Disclosures: **C. Chepkosgei:** None. **M. Solis:** None. **P. Sabandal:** None. **K. Han:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.11/E17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NIGMS 1R16GM145548
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NIH NIMH R21MH109953
Orville Edward Egbert, M.D. Endowment fund (UTEP)
Office of Research Sponsored Project (UTEP)
U-RISE NIGMS# 1T34GM145529 01

Title: The role of integrin in aging-related loss of inhibitory control

Authors: *A. P. BALLESTEROS SANCHEZ, D. MURILLO, P. SABANDAL, K.-A. HAN; Univ. of Texas at El Paso, El Paso, TX

Abstract: Progressive cognitive decline including impairments in inhibitory control and memory are key clinical manifestations of Alzheimer's disease and related dementias (ADRD). Although, substantial progress has been made about our understanding of ADRD pathophysiology (i.e., β-amyloid aggregation and hyperphosphorylated tau accumulation) the underlying mechanisms remain incomplete. We hypothesize that the interaction of genetic and non-genetic risk factors is important for ADRD. To test the hypothesis, we conducted an unbiased functional genetic screen to discover novel ADRD genes interacting with non-genetic factors (i.e., aging and social stress)in Drosophila. One of the ADRD genes we identified is inflated (if), which codes for one of the alpha integrin subunits. The overarching goal of this study is to identify how if causes dementia in an aging-dependent manner. Alpha integrin is a cell adhesion molecule and is involved in many developmental processes like cell migration. Yet, its role in aging and dementia is unknown. To address this knowledge gap, we examined the inhibitory control capacity of theheterozygous if (if/+) mutants across different ages (4 days, 2 weeks and 4 weeks old) using aGo/No-Go test. We found that the 4 days old if/+ displayed robust movement suppression similar to the wild-type Canton-S (CS). At 2 weeks and 4 weeks old, however, the if/+ exhibitedsignificantly augmented levels dysfunctional inhibitory control compared to CS. We also found that the hypomorphic if mutants have altered structural integrity of the mushroom body lobes, which are important for inhibitory control as well as learning and memory. We are currently testing the notion that if in the mushroom body neurons plays an important role in the aging-dependent loss of inhibitory control and the progress in this study will be presented. The findings of our study will provide novel insights on the role of alpha integrin in aging and ADRD.

Disclosures: A.P. Ballesteros Sanchez: None. **D. Murillo:** None. **P. Sabandal:** None. **K. Han:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.12/E18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant R00AG055683
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Interdisciplinary Neuroscience Program, University of Rhode Island
First-Year Doctoral Fellowships, University of Rhode Island
RI-INBRE SURE & SURF Programs, University of Rhode Island

Title: The role of DNA damage-induced epigenetic alterations in age-related cognitive decline and Alzheimer's disease

Authors: *S. BARTMAN, L. GASPAR, H. TOBIAS-WALLINGFORD, D. ZAMOR, G. COPPOTELLI, J. M. ROSS;
George and Anne Ryan Inst. for Neuroscience; Col. of Pharm., Univ. of Rhode Island, Kingston, RI

Abstract: Recent decades have witnessed a dramatic increase in human longevity, which has contributed to higher prevalence of age-related diseases including brain aging disorders, such as Alzheimer's disease (AD). The aging process is accompanied by an accumulation of damage to macromolecules, organelles, and cells, which ultimately leads to organ/tissue dysfunction and death. Although the precise cause of the aging process is unknown, epigenetic alterations and deregulation of gene expression have been implicated in playing a role. Using the innovative ICE (inducible changes to the epigenome) mouse model together with the well-characterized APP/PSEN1 (APP/PS1) mouse, we are directly testing, for the first time, whether epigenetic alterations induced by DNA damage, can affect the onset and progression of AD pathology in "DICE" (dementia from inducible changes to the epigenome) mice. A battery of behavioral testing is ongoing to compare possible cognitive changes in DICE mice with APP/PS1/CRE, ICE, and CRE controls. Preliminary results thus far indicate that male and female DICE mice move significantly more and with faster speed than controls, when assessing spontaneous locomotion in the open field behavioral assay. Using the startle reflex behavioral assay to evaluate brainstem functioning, both male and female DICE mice demonstrated a larger motor response following various auditory stimuli, as compared to controls. Ongoing studies aim to characterize and quantify Aβ; plaque formation as well as gliosis and microglial expression in brains from DICE mice as compared to APP/PS1/CRE controls using immunohistochemistry, western blot, ELISA, and qPCR. These findings will provide valuable insights into the etiology of Alzheimer's disease, especially as it pertains to the role of epigenetics.

Disclosures: S. Bartman: None. **L. Gaspar:** None. **H. Tobias-Wallingford:** None. **D. Zamor:** None. **G. Coppotelli:** None. **J.M. Ross:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.13/E19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Orville Edward Egbert, M.D. Endowment fund
NIGMS 1R16GM145548-01
U-RISE NIGMS #T34GM145529

Title: The dementia gene Scully and its role in the mitochondria

Authors: *M. SOLIS, C. CHEPKOSGEI, P. R. B. SABANDAL, K.-A. HAN;
Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract: Dementia has complex etiology that involves both genetic and non-genetic risk factors. How these risk factors interact for dementia remains poorly understood. To address this gap in knowledge, we conducted an unbiased genetic screen to identify novel dementia genes that interact with non-genetic risk factors (i.e., aging and social context) in *Drosophila melanogaster*. We identified *Scully* as a new genetic factor for dementia. *Scully* is the homolog of human 17-β-hydroxysteroid dehydrogenase 10, which is a multifunctional mitochondrial enzyme. We found that flies with the heterozygous mutation in *Scully* (*Scu/+*) exhibited deficits in inhibitory control and short-term memory in an aging-dependent manner. To determine the underlying mechanism, we focused on the potential role of *Scu* in mitochondria. We found no gross difference in mitochondria content in the aged *Scu* mutant and control brains. We are currently examining mitochondria dynamics, bioenergetics, and oxidative stress. Our study will provide novel insight on how genetic and non-genetic risk factors interact for dementia.

Disclosures: M. Solis: None. **C. Chepkosgei:** None. **P.R.B. Sabandal:** None. **K. Han:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

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Program #/Poster #: PSTR257.14/E20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant AG0577277
AARF-16-443173

Title: Unc5c T835M mutation-mediated neurodegeneration in late-onset Alzheimer’s Disease in a novel mouse model

Authors: *D. KARUNAKARAN[1], M. LEY[1], J. GUO[1], A. KHATRI[1], A. UPADHYAY[1], J. POPOVIC[1], D. PROCISSI[2], R. WATTS[3,4], J. ATWAL[3], J. SAVAS[1], R. VASSAR[1];
[1]Neurol., [2]Ctr. for Preclinical Imaging Core facility, Northwestern Univ., Chicago, IL;
[3]Neurosci., Genentech, South San Francisco, CA; [4]Denali Therapeut., South San Francisco, CA

Abstract: Alzheimer's disease (AD) is characterized by amyloid plaques, neurofibrillary tangles, and synaptic and neuronal loss. Recently, a rare autosomal dominant coding mutation, T835M, was discovered in the Un-coordinated 5c (*Unc5c*) netrin receptor gene that segregated with late-onset AD (LOAD). T835M alters a conserved amino acid in the hinge region of the Unc5c death domain, suggesting the mutation may increase apoptosis. Indeed, in primary hippocampal neurons, overexpression of Unc5c T835M increased cell death in response to neurotoxic stimuli including beta-amyloid (Aβ). These results suggest a mechanism by which Unc5c T835M may confer increased risk of LOAD, however the effects of this mutation in an AD animal model have not yet been explored. We hypothesize that the T835M mutation predisposes to LOAD by exacerbating neuronal death via increased sensitivity to Aβ-induced neurotoxicity and UNC5C death domain activation. Toward this end, we generated a mouse knock-in (KI) model of Unc5c T835M and crossed it with the NLGF mouse model of amyloid pathology and neuron loss. Our preliminary results show that homozygous KI mice have significantly reduced hippocampal volume, increased ventricular volume, dendritic disorganization (CA1 region) and reduced Unc5c protein level by 12-18 months of age. Further, we show that the neuronal cell death is observed in the KI mice by 12 months of age by TUNEL analysis and activated Caspase 3/7 activity assay. Additionally, KI mice also show morphological changes in the astrocytes with increased number of branched processes and reduced GFAP levels. Proteomics analysis of KI and wildtype hippocampal samples corroborate the biochemical and histological results which showed upregulation of oxidative stress and downregulation of chaperone proteins at 18 months. We are further investigating mechanisms of cell death and distal phenotypes in NLGF KI; Unc5c T835M KI mice by biochemical, cellular, and unbiased proteomics approaches. We expect our results to provide valuable insight into the molecular mechanism of UNC5C T835M mutation-mediated Aβ-associated cell death, and thereby identify novel therapeutic targets to prevent neuron loss in AD.

Disclosures: D. Karunakaran: None. **M. Ley:** None. **J. Guo:** None. **A. Khatri:** None. **A. Upadhyay:** None. **J. Popovic:** None. **D. Procissi:** None. **R. Watts:** None. **J. Atwal:** None. **J. Savas:** None. **R. Vassar:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NIMHD 3U54MD007592-29S5
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Orville Edward Egbert, M.D. Endowment fund (UTEP)
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Brain & Behavior Research Foundation

Title: Scully interacts with ecdysone in inhibitory control deficit

Authors: *P. SABANDAL, M. SOLIS, C. CHEPKOSGEI, K.-A. HAN;
Univ. of Texas, El Paso, El Paso, TX

Abstract: Scully (Scu) is linked to Alzheimer's disease (AD) because it binds to Aβ peptides and is overexpressed in the postmortem brains of AD patients. However, there is no study demonstrating that Scu contributes to AD in vivo. To narrow this knowledge gap, we investigated the role of Scu in dementia by measuring inhibitory control and memory in *Drosophila*. We found that the Scu-deficient flies exhibit aging-associated inhibitory control deficit and memory loss. We also identified the mushroom body as the major neural site for Scu's role in the aging-associated cognitive decline. Scu is the multifunctional mitochondrial enzyme HSD17β10 and is known to be involved in neurosteroid homeostasis in mammals and tRNA processing in *Drosophila*. We examined which Scu's function is important for its role in dementia. We found no genetic interaction of Scu with t-RNA processing molecules but found strong interaction with ecdysone, a major steroid hormone in *Drosophila*, metabolic enzymes. Specifically, the Scu mutant's phenotype in inhibitory control was aggravated by lessening ecdysone biosynthesis and reduced by decreasing ecdysone breakdown. Our findings will advance the knowledge of how Scu contributes to AD pathogenesis.

Disclosures: P. Sabandal: None. **M. Solis:** None. **C. Chepkosgei:** None. **K. Han:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.16/E22

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01NS095799

Title: Teasing apart a bi-level neuronal function for Tip60 HAT at the chromatin and RNA level.

Authors: *C. THOMAS, A. BHATNAGAR, F. ELEFANT;
Drexel Univ., Philadelphia, PA

Abstract: The histone acetyltransferase (HAT) Tip60 is an essential epigenetic mediator of neuronal transcriptional regulation and is implicated in Alzheimer's disease (AD). Tip60 contains a catalytic HAT domain that promotes histone acetylation mediated chromatin control and a chromodomain (CD) that interacts with methylated histone lysine residues. Recently, our

lab reported a novel RNA binding function for Tip60 that is localized within its CD and underlies neuronal RNA alternative splicing (AS) regulation in the brain. AS of RNA is a process that enables brain cells to generate different functional variants of the same protein to promote the protein diversity required for dynamic brain function in making new memories. Recent reports highlight defects in RNA splicing of genes in the brains of AD patients, thus making splicing disruptions a widespread hallmark of AD. Unfortunately, causes for these splicing disruptions in the brain are currently unknown. To further elucidate Tip60's RNA binding/splicing function, we carried out high resolution homology modeling and molecular visualization of Tip60's chromodomain (CD). Our results strongly predict the RNA binding loop within Tip60's CD is critical for direct Tip60-RNA interaction. To tease apart Tip60's RNA versus histone binding function in neural gene control and cognition, we mutated highly conserved amino acids (a.a) in Tip60's CD strongly predicted to specifically interact with either histones ($Tip60^{mutHis}$) or RNA ($Tip60^{mutRNA}$) and generated transgenic flies carrying these inducible mutant Tip60 constructs. These transgenic $Tip60^{mutRNA}$ and $Tip60^{mutHis}$ fly models will serve as powerful tools to tease apart neural functions dependent upon histone vs. RNA binding or both. We will induce expression of mutant Tip60 in the fly brain and carry out functional assays to assess cognitive ability using both larval (single odor paradigm) and adult (olfactory shock learning) learning and memory assays as well assess brain morphology using immunohistochemistry with well characterized markers. We will also assess gene expression using RNA-Seq, Tip60 splicing activity using rMATs on RNA-Seq data, and chromatin and RNA binding using ChIP and RIP, respectively. We anticipate that RNA versus histone binding functions are required for specific functional outputs and some neuronal processes will be more dependent on a given Tip60 binding function than others. Our results will elucidate a new bi-level regulatory role for Tip60 in chromatin and RNA that has potential to transform how researchers view Tip60 HAT mediated neural gene control in the context of cognition and AD.

Disclosures: **C. Thomas:** None. **A. Bhatnagar:** None. **F. Elefant:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.17/E23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Madrid Government SI2/PBG/2020-00014

Title: Reduced euchromatin and increased facultative heterochromatin in advanced Alzheimer's disease in human postmortem brain tissue

Authors: *A. UCEDA-HERAS, C. CAVADA, M. GARCÍA-CABEZAS;
Anatomy, Histology and Neurosci., Univ. Autonoma de Madrid, Madrid, Spain

Abstract: Gene expression in the human cerebral cortex seems to be increased in mild cognitive impairment and early Alzheimer´s disease (AD) stages. In contrast, in advanced AD stages there is marked gene expression decrease in cortical areas. This apparent paradox could be mediated by a time-course of epigenetic modifications in the nuclei of cortical neurons in parallel to AD progression. To address this question, we quantified the expression of two posttranslational histone modifications, H3K27-trimethylated histone (H3K27me3), which marks facultative heterochromatin, and H3K4-mono/di/trimethylated histone (H3K4me1/2/3), which marks euchromatin, in postmortem human brain tissue of neurotypical subjects and early (Braak II) and advanced (Braak V) AD cases. We used immunohistochemistry to label H3K27me3 and H3K4me1/2/3 in human temporal lobe intact tissue because it allows the quantification of histone modifications by layer and cortical type; thus, we parcellated the human temporal neocortex in mesocortical (agranular, dysgranular) and isocortical (eulaminate I, eulaminate II, eulaminate III, and koniocortex) types and measured the immunostaining of H3K27me3 and H3K4me1/2/3 across layers III, IV, and V of all neocortical types. We found that the expression of H3K27me3 increased in Braak II AD stage; this increase was statistically significant in isocortical areas that are not involved by AD pathology at this stage ($p<0.05$). In Braak V AD stage, H3K27me3 expression increased in a subpopulation of pyramidal layer III neurons in mesocortical and eulaminate I and II types; all these types are severely affected by AD pathology at this stage. We also found that the expression of H3K4met1/2/3 was higher in layers III, IV, and V of eulaminate III and koniocortical types in Braak II AD stage ($p<0.01$); in contrast, in Braak V AD stage, H3K4met1/2/3 expression decreased across all cortical layers and types ($p<0.01$). We conclude that histone marks related to euchromatin increase in cortical neurons in early AD stages and decrease in advanced AD stages; in parallel to these changes, histone marks that are related to facultative heterochromatin increase in advanced AD stages in a subpopulation of layer III pyramidal neurons, specifically, in mesocortical and eulaminate I and II types. Our findings highlight the need for postmortem human brain studies using intact tissue to characterize the progression of epigenetic modifications by cortical type and layer in parallel to AD stages.

Disclosures: **A. Uceda-Heras:** None. **C. Cavada:** None. **M. García-Cabezas:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1 AG056499
NIH UF1 AG057707
NIH R01 AG053983
NIH P30 AG062429
NIH UL1 TR001442

Title: Potential relevance of SNPs in linkage disequlibrium with APOE variants identified by genome wide sequencing

Authors: *S. D. EDLAND[1], C. NASAMRAN[2], K. FISCH[2];
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Abstract: It is an open question whether cis acting transcription factors in linkage disequilibrium with the known Alzheimer's disease risk variant missense mutations on the apolipoprotein E (*APOE*) gene are relevant to disease expression. To investigate this, we performed haplotype analysis of genome wide sequencing (GWS) data from 456 subjects (220 Alzheimer cases and 236 normal controls) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. SNPs in the region of chromosome 19 spanning from *TOMM40* to the multiple enhancer region *ME.2* immediately distal to *APOC1* were assessed for association with the *E2* and *E4* variants rs7412 and rs429358 on *APOE*. Identified variants were queried against expression quantitative trait loci databases, including RegulomeDB, SNP2TFBS, MEME, and BRAINEAC. We identified a haplotype block including the *E2* rs7412 variant SNP associated with Alzheimer's disease. Twelve of 12 SNPs defining this haplotype are flagged by the Regulome database as potential gene expression regulatory loci, including a SNP in the ME.1 multiple-enhancer region shown to affect APOE expression levels in astrocytes (rs483082), and including a SNP within a putative RNA polymerase II subunit Rpb1 binding region (SNP rs1065853). SNP rs483082 is a common variant strongly associated with Alzheimer's disease within the ADNI sample (minor allele OR=0.43, p=6.0e-9). SNP rs1065853 is in near perfect disequilibrium with *APOE E2* (R-squared 0.97 versus rs7412) and is more strongly associated with Alzheimer's disease than is *APOE E2* rs7412 within the ADNI sample (odds ratio=0.25, p=6.7e-5 versus odds ratio=0.27, p=2.5e-4). A number of polymorphisms in linkage disequilibrium with *APOE* risk alleles affect transcription factor binding sites and regulatory regions. It is plausible that these potentially functional polymorphisms contribute to disease risk beyond the risk conferred by the *E2* and *E4* missense mutations on *APOE*.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.19/E25

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CAPES PrInt: Program for Institutional Internationalization

Title: Investigating the Relevance of Genetic Variation at Post-Translational Modification Sites in the Polygenic Risk Model for Alzheimer's disease-associated Phenotypes

Authors: *S. PACO[1], F. PEREIRA[2], S. ANDREWS[3], L. T. GRINBERG[4], M. NASLAVSKY[5];
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Abstract: Alzheimer's disease (AD) is projected to become three times more prevalent by 2050, contributing to the escalating global burden of dementia. Recent advancements in biotechnology have sparked significant interest in early detection, prevention, and capitalizing on genetic characteristics for patient stratification. A Genome-wide association studies (GWAS) research have identified more than 80 loci associated with AD explaining 53-70% of heritability. Polygenic risk score (PRS) aggregates the effect of multiple genetic variants to provide an estimate of genetic liability for a trait. However, the clinical implementation of PRS necessitates refinements, such as the incorporation of genetic loci with functional annotation spanning post-translational modifications (PTMs), chromatin data, and variants associated with quantitative expression traits. This study aims to investigate the impact of genetic variation on potential PTMs target sites to improve risk prediction in AD. In this work the PRS were constructed using the largest AD GWAS to date (n= 63,926) as the base dataset, the Alzheimer's Disease Neuroimaging Initiative (ADNI) (n= 808) as the target dataset, and PRSice. Using PLINK, we performed a comprehensive filtering process and quality control assessment, keeping 4.8 and 6.3 million variants in the base and target files respectively, 760 samples remained. PRSice implements a clumping and threshold model - r2 :0.1, window size: 250 kb, over p-value thresholds ranging from 1 to 10−8. The optimal theshold was 1.4 e-08.. Logistic regression was used to evaluate the predictive performance of the AD-PRS (PRSz thereshold-0.55) yielding a sensitivity and specificity of 0.9 and 0.18, respectively, and the accuracy of the prediction was found to be 0.65. As this initial phase of the study primarily focused on GWAS array genotyping variants with reasonable precision, we hypothesize that PTM annotations (accessible only in sequencing datasets) are likely to enhance the correctness by upweighting coding variants in a PRS. In conclusion, these preliminary results establish a pipeline for further investigations, emphasizing the significance and potential of incorporating additional analyses and relevant information to improve the precision and reliability of PRS in AD risk prediction. We will focus on innovative approaches for filtering genetic variants and incorporating additional biological functional information of PTMs.

Disclosures: S. Paco: None. **F. Pereira:** None. **S. Andrews:** None. **L.T. Grinberg:** None. **M. Naslavsky:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.20/E26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: U54 AG054345

Title: Identifying human-relevant genetic interactors of APOE using genetically diverse mouse strains

Authors: *K. ELK[1], K. D. ONOS[1], A. UYAR[2], K. KEEZER[1], R. KASPER[1], O. MAROLA[1], D. GARCEAU[1], R. PANDEY[1], G. W. CARTER[1], G. HOWELL[1], M. SASNER[1];
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Abstract: *APOE$^{\varepsilon 4}$* is the greatest genetic risk factor for late-onset Alzheimer's Disease (AD), and recent work has introduced human *APOE* variants in classical laboratory mouse strains, typically the C57BL/6J (B6J). While this has led to advances in our understanding of *APOE* biology, it is known that risk encoded by *APOE$^{\varepsilon 4}$* can differ dependent on other genetic factors present. We have previously shown that AD mouse models on genetically diverse wild-derived mouse strains demonstrate robust differences in immune response to amyloid and neurodegeneration, better representing the phenotypic spectrum of AD than previous models. Therefore, we seek to use these models to identify human-relevant genetic interactors of *APOE* within disparate genetic contexts and in the presence/absence of amyloid. Mice were developed by backcrossing *B6J.APOE$^{\varepsilon 4}$* to the respective wild strain (PWK/PhJ, WSB/EiJ) for 5 generations and then were crossed with congenic APP/PS1 carriers of each respective strain. This led to characterization of cohorts of 4- and 8-month males and females homozygous for *APOE$^{\varepsilon 4}$*, with and without hemizygous *APP/PS1*. Transcriptional profiling of brain hemispheres was performed, followed by neuropathological assessments via immunofluorescence (IF) and plasma measurement of key biomarkers such as Neurofilament Light (NfL). Data were assessed for strain-, genotype-, and age-specific variation. Differential expression (DE) analysis of transcriptomic data indicated that *APOE$^{\varepsilon 4}$* homozygosity was the greatest source of variation, independent of amyloid, in 4- and 8-month PWK animals. In addition, neurodegeneration in multiple cortical regions was identified via IF in 8-month (but not 4-month) PWK *APOE$^{\varepsilon 4}$* homozygotes, a finding which was again independent of *APP/PS1* genotype. Preliminary IF results also show a significant increase in the prevalence of disease-associated microglia (DAMs) in APP/PS1 brains as expected, but DAM response to amyloid is significantly attenuated by *APOE$^{\varepsilon 4}$* homozygosity in PWK animals. *APOE$^{\varepsilon 4}$* increased the incidence and severity of cerebral amyloid angiopathy (CAA) in transgenic mice regardless of background. Further neuropathological assessments are ongoing and will be correlated with DE results. Overall, we use neuropathology and transcriptomics to identify potential interactors of *APOE* by utilizing natural genetic variation, describe varying effects of AD's most potent genetic risk factor dependent on genetic context and promote the incorporation of genetically diverse mouse strains in the study of complex neurodegenerative disorders such as AD.

Disclosures: K. Elk: None. **K.D. Onos:** None. **A. Uyar:** None. **K. Keezer:** None. **R. Kasper:** None. **O. Marola:** None. **D. Garceau:** None. **R. Pandey:** None. **G.W. Carter:** None. **G. Howell:** None. **M. Sasner:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.21/E27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH National Institute of Aging
Cure Alzheimer's Fund
Alzheimer's association

Title: Identification of entorhinal cortex neuron subpopulation markers

Authors: *A. MORELLO, H. KAHVECIOGLU, C. DIMOVASILI, J.-P. ROUSSARIE; Boston Univ. Grad. Program In Anat. & Neurobio., Boston, MA

Abstract: The entorhinal cortex (EC) is the first brain region to be selectively affected by neurofibrillary tangles (NFT) in preclinical stages of Alzheimer's disease (AD). Precisely, NFT start accumulating in the layer II of the transentorhinal cortex. Because the EC is a very heterogeneous region in terms of connectivity, cytoarchitecture, and function, a prerequisite to understand how gene expression determines vulnerability is the generation of a precise molecular atlas of the region. Our previous work provides evidence of conservation of EC layer II cell-types between mouse and humans (Roussarie et al., Neuron, 2020). However, gaining insight into EC layer II neuron subtypes and the degree to which these are conserved in a species closer to humans is necessary. Therefore, guided by our previously generated mouse atlas of the EC, we aim to create a comprehensive atlas of the EC in macaque. Using in situ hybridization, we studied whether previously identified neuronal subpopulations distributed along the dorsal-ventral axis of mouse EC layer II were conserved in macaque. We identified conserved neuronal subpopulations markers in macaque EC, and observed distinct distributions of neuronal subpopulation markers along the medial-lateral axis. Furthermore, we investigated whether these markers were conserved with sex and age. Overall, this atlas will set the basis for the characterization of the different neuronal subpopulations and subregions of the EC, significantly advancing our understanding on how cellular identity might play a role in AD vulnerability.

Disclosures: A. Morello: None. **H. Kahvecioglu:** None. **C. Dimovasili:** None. **J. Roussarie:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.22/E28

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH U54AG054349

Title: Phenotypic characterization of a novel Bin1^{K358R} mouse model of Alzheimer's disease

Authors: *A. GOMEZ ARBOLEDAS, L. FERNANDEZ GARCIA-AGUDO, S. KAWAUCHI, C. DA CUNHA, G. MILINKEVICIUTE, K. TRAN, A. TENNER, F. LAFERLA, G. MACGREGOR, K. GREEN;
Univ. of California, Irvine, Irvine, CA

Abstract: Background: Bridging integrator 1 (BIN1) has been identified as a genetic loci directly associated to the risk of developing late-onset Alzheimer's Disease (AD). Several SNPs in the BIN1 gene have been identified by Genome-Wide Association Studies (GWAS), including the rare BIN1 coding variant rs138047593 (K358R). Different BIN1 isoforms are involved in a wide range of functions, including endocytosis or membrane remodeling, among others. However, the role of BIN1 during AD pathogenesis is still controversial as it's been shown to be involved in amyloid- β production by targeting BACE1, but it has also been described its potential contribution to the spreading of Tau aggregates by modulating the endocytic pathway. Here, in an effort to understand the impact in brain biology of different LOAD risk variants as well as with the objective of developing more accurate and valuable mouse models for Alzheimer's Disease, the UCI MODEL-AD group has developed a novel mouse model with the $BIN1^{K358R}$ variant. **Method**: By using CRISP/Cas9, we have generated $BIN1^{K358R}$ mice that carry a coding mutation corresponding to the rs138047593 SNP found in human BIN1. We then crossed the BIN1 mice with the 5xFAD mouse model of AD and aged them to 4 and 12 months of age. Mice were prefursed, and brains were harvested and further processed for bulk RNAseq, MSD and IHC analysis. Confocal images were further analyzed by Imaris sorftware in order to quantify amyloid plaques and glial cells. **Results**: At 4 months, 5xFAD;$BIN1^{K358R}$ showed a significant reduction in amyloid plaques as well as a significant reduction in microglial cell density compared to 5xFAD mice. However, at later stages of the disease (12 months of age), we observed a significant increase on amyloid pathology in the 5xFAD;$BIN1^{K358R}$ mice, but no changes in the microglial response towards these plaques were further detected. Interestingly, at 12 months of age, we observed an impaired astrocytic and oligodendrocytic response towards these amyloid plaques in the 5xFAD;$BIN1^{K358R}$ when compared to 5xFAD mice. Finally, reduced levels of plasma and brain NfL were also detected at 12 months of age in 5xFAD mice carrying the $BIN1^{K358R}$ variant. **Conclusion:** Our results indicate that the $BIN1^{K358R}$ variant has a profound effect on Aβ deposition in the 5xFAD mouse model of AD. Moreover, the BIN1 variant resulted in an impaired astrocytic and oligodendrocytic response towards these amyloid plaques, which in turn correlates with reduced levels of NfL.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.23/E29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: U54 AG065187

Title: Discovery Of New Alzheimer's Disease Therapeutic Targets: Knowledge Graph Approach

Authors: *S. KEEGAN[1], G. CARY[1], R. TRIPATHY[2], J. WILEY[3], H. WANG[2], T.-A. .[4], Y. LI[2], G. W. CARTER[1];
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Abstract: Background: Alzheimer's disease (AD) therapeutics have largely been unsuccessful in alleviating disease burden, potentially due to a narrow focus on limited disease mechanisms. The TREAT-AD Consortium is identifying novel molecular targets for AD from underexplored areas of disease linked pathology. Method: We created 19 knowledge graphs (KGs) representing distinct endophenotypes of AD, each with annotated protein-protein interactions connecting genes. The gene nodes were characterized by multi-omic data and Gene Ontology (GO) annotations, and the edges were scored for confidence. A weighted Key Driver Analysis (wKDA) predicted causal nodes within each KG. A Graph Neural Network (GNN) using the KGs as a base network predicted how key drivers affect clinical phenotypes. Result: KGs included key AD processes such as immune response, mitochondrial metabolism, and oxidative stress. The overlap in causal genes for endolysosome and lipid metabolism identified CLTC and DAB2 as common driver proteins, particularly in their regulation of clathrin-coated endocytic vesicles and clathrin-coated vesicle membranes. These and other key connections are proposed as targets for further therapeutic studies. Conclusion: Alzheimer's Disease biology were subdivided into networks which represent molecular processes consistently altered in AD cases. Genes from these networks were prioritized to identify candidate therapeutic targets that are well situated to affect the network biology. TREAT-AD will next validate these targets in cell models and generate experimental resources to support further target development.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.24/E30

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG076235

Title: Expression and Regulation of EZH2: Implications in Brain Aging and AD

Authors: *K. DENNEY[1], Y. LEI[2], Q. DU[2], X.-Y. LU[2];
[1]Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA; [2]Neurosci. and Regenerative Med., Med. Col. of Georgia At Augusta Univ., Augusta, GA

Abstract: Epigenetic regulation plays an important role in aging and AD pathology. Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of polycomb repressive complex 2 (PRC2), which catalyzes histone and DNA methylation. Dysregulation of histone modifications and DNA methylation has been implicated in the aging process and the development of AD. The goal of this study was to investigate age- and AD-related changes in EZH2 expression in mice. Immunostaining of EZH2 was performed on brain sections from C57BL/6J mice of various ages, including 5 months, 10 months, and 20 months, and 5xFAD mice of 3 months and 9 months of age. We demonstrated that total levels of EZH2 protein expression decreased in the hippocampus and prefrontal cortex of aged C57BL/6J mice and 5xFAD mice. Additional experiments involving western blot analysis and electron microscopy are currently in progress to quantify and localize EZH2 within different cellular compartments in the brains of both wild-type mice and 5xFAD mice of various ages. On-going experiments are focused on assessing the impact of AAV-mediated EZH2 overexpression in the aged brain on cognitive performance. Furthermore, primary neuronal culture was established to investigate the mechanisms underlying the regulation of EZH2 protein expression by oxidative insults. These studies will provide insights into the potential mechanisms underlying EZH2 dysregulation in aging and AD, particularly in relation to epigenetic contributions to cognitive impairment.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.25/E31

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Pathological characterization of the novel de novo APP Y681H Aros mutation

Authors: *S. ZAMPAR[1,2], S. LIBARD[6,9], M. BOCZAR[7], W. P. MICHNO[7], L. KILANDER[7], L. WU[2], S. E. DI GREGORIO[1,2], S. MASTRANGELO[1,2], G. GRIMMER[1,2], H. WANG[2], S. F. LICHTENTHALER[10,11], G. SCHRÖDER[12,13], J. C. WATTS[2,3], G. SCHMITT-ULMS[2,4], D. SEHLIN[9], D. SEHLIN[8], P. E. FRASER[2,5], N. DAHL[9], V. GIEDRAITIS[7], M. INGELSSON[1,2,7,4];
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and JuStruct, Jülich Ctr. for Structural Biol., Jülich, Germany; [13]Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

Abstract: Mutations in the amyloid precursor protein (APP) gene can cause early onset familial Alzheimer's disease (FAD) and/or cerebral amyloid angiopathy (CAA). In this study we analyzed pathological aspects of the novel *de novo* APP Y681H *Aros* mutation, identified by whole genome sequencing in a Swedish subject who presented with a large cerebral hemorrhage at the age of 55 and died at the age of 66. The brain from the *Aros* mutation carrier showed prominent amyloid-β (Aβ) plaque deposition in the cortex and abundant CAA. Because the mutation is located next to the BACE1 β'-cleavage site on APP and in proximity of neprilysin (NEP) and insulin degrading enzyme (IDE) Aβ cleavage sites, we analyzed how the *Aros* mutation affects APP processing, Aβ degradation and Aβ aggregation propensities *in vitro*. Besides wild type (WT) APP and Aβ, we included the *Leuven* (*APP* E682K) FAD mutant for comparison. HEK293 cells were transfected with vectors containing WT or *Aros APP* sequences, and levels of Aβ1-40 and Aβx-40 were measured in the cell supernatants with Aβ-specific ELISAs (n=3). Size exclusion chromatography was performed on synthetic Aβ peptides to isolate monomers. Serial dilutions of Aβ1-42 WT, *Aros* and *Leuven* monomers were incubated in triplicates at 37°C for 18 h in the presence of 20μM ThT to monitor their aggregation in a time-dependent manner. *In vitro* digestion of Aβ monomers was performed by incubation with recombinant NEP and IDE for 2 h at 37°C (n=3). The digested products were visualized by western blot and their band intensities quantified with Image Lab software. A significant increase of both Aβ1-40 levels and the ratio of Aβ1-40/Aβx-40 was measured in the supernatant of *APP Aros* transfected cells compared to *APP* WT. ThT aggregation assay data showed no changes in Aβ1-42 *Aros* aggregation kinetics compared to WT, while Aβ1-42 *Leuven* aggregated faster. Aβ1-42 *Aros* was digested to a lesser extent by NEP and IDE *in vitro* compared to Aβ1-42 WT and *Leuven*. Taken together, the *APP Aros* mutation, causing AD with CAA, appears to influence APP processing and increase Aβ production. Whereas no changes in aggregation propensities were seen for Aβ1-42 *Aros*, the variants appear to be less degradable, which, together with the altered APP processing, could lead to increased levels of Aβ in the brain. In ongoing experiments, we are assessing the deposit composition, structural features, and toxic properties of the *Aros* Aβ mutant.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.26/E32

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: U54 AG054345

Title: Assessing Brain Metabolic Network Pharmacodynamics of Aducanumab in 5xFAD Mice

Authors: *P. R. TERRITO[1], C. P. BURTON[2], S. C. PERSOHN[2], E. W. MINER[2], K. ELDRIDGE[2], S. K. QUINNEY[2], K. A. HAYNES[3], K. D. ONOS[5], M. SASNER[6], G. R. HOWELL[6], G. W. CARTER[6], A. OBLAK[2], B. T. LAMB[2], S. J. SUKOFF RIZZO[4];
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Abstract: Background: The Model Organism Development for Evaluation of Late Onset Alzheimer's Disease (MODEL-AD) Preclinical Testing Core (PTC) established a rigorous drug testing strategy for unbiased assessments of therapeutic agents. To validate this pipeline for therapeutic testing, the chimeric murinized antibody aducanumab (chAdu), was synthesized, qualified, and selected for evaluation in aged 5XFAD mice. To elucidate the pharmacodynamic (PD) impact on metabolic networks, functional connectomic modeling was performed. **Methods:** chAdu was synthesized by transfection and expression in TunaCHO™ cells and qualified by Size-Exclusion Chromatography and LC/MS/MS. To determine the safe and effective dosing strategy, PK studied were conducted in 9 mos 5XFAD mice of both sexes dosed with chAdu from 0.1 to 30 mg/kg, and blood sampled at 0, 1, 3, 7, 10, 14, 21, 24, and 27 days post administration. Based on PK/PD model simulations to predict dosing level and intervals, 9 mos male and female 5XFAD mice were dosed weekly at 0.1, 1.56, and 30 mg/kg. To assess brain metabolic network PD, mice were imaged at baseline and conclusion of chronic treatment via 18-FDG PET/CT. Images were segmented using the Paxinos-Franklin atlas and analyzed for network connectivity by z-score transformation, pairwise covariance analysis, and regional modularization via multi-resolution-consensus clustering (MRCC) of all 27 brain regions, where whole brain and module level statistics were conducted between sexes and across doses. **Results:** Analysis of synthesized chAdu showed high purity and stability with freeze/thaw cycles. PK/PD modeling revealed $T_{1/2}$ of ~2.5 days and informed the PD dose regimen (0.1-30 mg/kg Q1W, IP). 12-week treatment with chAdu resulted in dose- and sex-dependent dependent reversal of glycolytic loss in key brain regions. Whole brain covariance analysis of regional 18F-FDG PET uptake thresholded at the $p<0.05$ level, revealed a dose and sex dependent changes in network degree (nodal connections), density (network connections), positive and negative connection strength (nodal strength), and clustering coefficient (number of sub-networks). Brain network MRCC modules composition and distribution showed dose and sex dependency, indicating that chAdu altered brain network connectivity consistent with whole network analysis. **Conclusions:** These data indicate that chAdu was selective and stable, and resulted in sex and dose dependent relevant metabolic network changes consistent with neuromodulation, and thus demonstrate the value of metabolic connectomic modeling for evaluating drug efficacy.

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Poster

PSTR257. Alzheimer's Disease: Genetics

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.27/E33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: This research project was supported by CONAHCYT Grant: 319578. We are grateful for the Postdoctoral Fellowships from CONAHCYT (Dr.María del Carmen Silva-Lucero) and DGAPA (Dr. Laura Gómez-Virgilio).

Title: Impaired Autophagy Flux and Chaperone-Mediated Autophagy in Familial Alzheimer's Disease Fibroblasts.

Authors: *N. LUMBRERAS-ZAVALA, L. GOMEZ-VIRGILIO, M. SILVA-LUCERO, M. CARDENAS-AGUAYO;
Physiology, Sch. of Med., UNAM, Ciudad de México, Mexico

Abstract: Introduction. Alzheimer's disease (AD) is the most common cause of dementia, and it is histopathologically characterized by extracellular amyloid plaques composed of the Amyloid-β peptide (Aβ) and intracellular neurofibrillary tangles constituted by the hyperphosphorylated tau protein. Alzheimer's disease is classified into sporadic late-onset (LOAD) disease representing more than 99% of the cases, and familiar AD (FAD) or early-onset familial disease (EOAD), which represents 1% of the cases. FAD is caused by the autosomal dominant mutations in the AβPP, PS1, and PS2. Fibroblasts from FAD patients, with a mutation in PS1, have shown increased expression of the macroautophagy markers and alterations in signaling pathways related to cellular stress, autophagy, lysosomes, and tau phosphorylation (Lopez-Toledo et. al., 2022), additionally, a dysfunction in autophagy, and, chaperone-mediated autophagy (CMA) is related with neurodegenerative disorders, that is why, our study has the aim to evaluate the macroautophagy and CMA in FAD fibroblast. **Methods.** Skin Fibroblasts from FAD patients and non-affected individuals were obtained from the Coriell Institute (New Jersey) repository and cultured in Earl MEM salts medium with 15% non-inactivated FBS. The macroautophagy and CMA markers in these cells were characterized by Western blot, moreover, autophagy was induced by starvation and chloroquine addition to evaluate the autophagic activity and autophagic flux with Cyto-ID essay and PremoTM Autophagy Tandem Sensor respectively. **Results.** Autophagy Assays showed differences in the autophagy activity in the cells of FAD patients vs cells from healthy controls pointing to an increase in autophagy in FAD fibroblasts with very low autophagy flux. Western blotting of CMA markers showed downregulation in these markers. **Conclusion.** Autophagy activity and CMA markers showed dysregulation in the fibroblasts of FAD patients vs the cells of healthy individuals. These findings in peripheral cells could have the potential for early diagnosis, detection of new biomarkers, and drug testing.

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Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.28/E34

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant R01AG057914
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NIA Grant R01AG057914-03S1

Title: Linking cognitive and pathological resilience using brain-wide immunohistochemistry in the AD-BXD panel

Authors: *B. GURDON[1], N. HADAD[1], S. YATES[2], T. MURDY[1], M. PUCHADES[3], J. G. BJAALIE[3], K. O'CONNELL[1], C. C. KACZOROWSKI[4];
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Abstract: The relationship between regional cell composition, brain pathology, and memory impairment in Alzheimer's disease (AD) remains incompletely understood. The specific brain regions and tracts (and their interactions) that explain the heterogeneity of cognitive decline with AD are not clear. By integrating brain-wide immunohistochemistry and cognitive outcomes we can achieve unbiased detection of regions of interest (ROIs) and identify cellular correlates of cognitive resilience for causal testing. Immunohistochemistry (IHC) was completed to evaluate neurodegeneration (NeuN), gliosis (Iba1 & GFAP), amyloid beta (Aβ) pathology (AB1-42), and cell bodies (Thionine) in adult (6 months (m)) and middle-aged (14m) mice of the AD-BXD genetic reference panel (n=228). Using the QUINT workflow, hemibrain slices were systematically segmented and registered to the Allen Brain Atlas to gain a global perspective of percent cell and pathology coverage. IHC traits were correlated with contextual fear conditioning outcomes to identify regions whose stain composition is associated with memory performance. Contrary to our prior work using ELISA-based Aβ measurement, we find that Aβ quantified via IHC at the presymptomatic time point (6m) is strongly correlated with differences in short- and long-term memory in 14m female 5XFAD carriers. Furthermore, the degree of astrogliosis at 6m in cortical, striatal, and thalamic regions acts as a predictor of cognitive outcomes at 14m. While age-related decreases in NeuN load were not observed, wide variation in neurodegeneration levels could be attributed to strain differences, and 14m NeuN load was positively correlated with 14m long-term memory among this female 5XFAD population. Highlighting the importance of genetic background on AD progression, we were able to categorize strains as resilient or susceptible to pathological and cognitive decline and evaluate the overlap of these traits. Strains that exhibit the unique identity of being pathologically susceptible but cognitively resilient offer a novel opportunity to investigate the underlying mechanisms of protection from cognitive decline with AD. In conclusion, by integrating brain-wide IHC and behavioral data, we were able to identify regional and cellular correlates that may predict downstream cognitive outcomes. Detection of these biomarkers may prove a valuable resource to disseminate the

insidious prodromal stages of AD in which biochemical changes precede apparent clinical symptoms.

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Poster

PSTR257. Alzheimer's Disease: Genetics

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.29/E35

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: G-RISE Grant #226141373A
NIH NIGMS 1R16GM145548
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Brain & Behavior Research Foundation

Title: The role of Frequenin 1/Neuronal calcium sensor 1 in inhibitory control

Authors: *A. PIZANA[1], K. M. LOYA[1], P. B. SABANDAL[2], K.-A. HAN[3];
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Abstract: The role of Frequenin 1/Neuronal calcium sensor 1 in inhibitory control
Aldo Pizana, Kimberly Loya, Paul Rafael Sabandal and Kyung-An Han
Inhibitory control is a cognitive process which enables organisms to suppress inappropriate thoughts and actions, allowing them to properly execute goal-driven behaviors. The mechanism underlying inhibitory control is not fully understood. To address this gap in knowledge, we conducted a screen to identify genes that interact with the dopamine system for inhibitory control using a Go/No-Go test in *Drosophila*. One of the genes we discovered is *Frequenin 1* (*Frq1*). Specifically, the heterozygous mutant *Frq1* (*Frq1/+*) or dopamine transporter mutant *fumin* (*fmn/+*) exhibited robust movement inhibition in Go/No-Go test while the double heterozygous *Frq1/+; fmn/+* mutant showed dysfunctional inhibition. Frq1 codes for a calcium-binding protein and is a homolog of the mammalian neuronal calcium sensor 1 (NCS-1). Frq1 is known to regulate synaptic transmission and plasticity during development, but our study is the first to reveal the role frq1 in adult brain function. The goal of this study is to identify how the Frq1-dopamine interaction leads to loss of inhibitory control. We found that the Frq1 mutant brains have less tyrosine hydroxylase (the rate-limiting enzyme for dopamine biosynthesis) compared to controls. We are currently investigating how Frq1 mutation affects dopamine neurons and their postsynaptic mushroom body neurons. Our finding will advance our understanding on the

role of Frq1 in inhibitory control.
Key words: Neuronal calcium sensor 1, inhibitory control, dopamine

Disclosures: **A. Pizana:** None. **K.M. Loya:** None. **P.B. Sabandal:** None. **K. Han:** None.

Poster

PSTR257. Alzheimer's Disease: Genetics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.30/E36

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1RF1NS112391-01

Title: Investigating retrotransposon-derived circular DNA as a driver of neuroinflammation in Alzheimer's disease and related tauopathies

Authors: *M. E. LAMBERT;
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Abstract: Transposable elements, or “jumping genes,” have the ability to mobilize within the genome. Retrotransposons, the largest class of transposable elements, are thought to have derived from ancient retroviral infections that involved insertion of viral genomes into the germline and thus became fixed within the human genome. While transposable elements comprise of 45% of the human genome, the vast majority are transcriptionally silenced due to their localization within heterochromatin and post-transcriptionally silenced by cellular defense mechanisms involved in the innate immune response. In Alzheimer’s disease and related tauopathies, pathogenic forms of tau protein destabilize the nucleoskeleton, causing heterochromatin to decondense. Opening of the heterochromatin causes previously silenced genes, such as retrotransposons, to be aberrantly transcribed. Retrotransposon activation involves transcription of host retrotransposon DNA and reverse transcription into a new DNA copy. Such DNA copies can exist in an episomal state or be inserted into the genome. Episomal DNA is detected by the cell and activates the innate immune response, driving intracellular inflammation and subsequent cell death. Previous work from our lab and others report that tau transgenic mice and Drosophila have increased retrotransposon DNA copy number. In preliminary studies, we find increased retrotransposon DNA copy number in human patients with Progressive Supranuclear Palsy, a primary tauopathy. While these studies suggest retrotransposon transcripts have been reverse-transcribed, we do not currently know whether this copy number increase can be attributed to genome insertion or extrachromosomal activity. We are utilizing frontal cortex brain lysate from human patients with tauopathy to investigate circular DNA as a potential source of increased retrotransposon DNA copy number and a driver of intracellular inflammation.

Disclosures: **M.E. Lambert:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.01/E37

Topic:

Support: NIH / National Institute on Aging funding P01AG026572 to RDB
NIH / National Institute on Aging funding 1T32AG061897 to RDB
Center for Innovation in Brain Science to RDB

Title: Molecular profiles of precision midlife combinatorial therapy in hAPP hAPOE risk model of AD

Authors: *H. VAN ROSSUM[1,2], G. TORRANDELL[2,1], E. REYES-REYES[2,1], Y. SHANG[2,1], R. D. BRINTON[2,1];
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Abstract: Determinants of late-onset Alzheimer's disease (LOAD) are multifactorial. While age, sex and APOE4 genotype remain the leading non-modifiable risk factors, other modifiable conditions including hypercholesterolemia, type-two diabetes (T2D), and increased peripheral inflammation contribute to disease progression. Preliminary bioinformatic analysis of Alzheimer's Disease Coordinating Center (NACC) data indicated that patients using a combination of lipid lowering, T2D, and anti-inflammatory therapies exhibited greatest resilience to cognitive decline based on mini-mental state exam (MMSE) score. Determining the molecular impact of combination therapy is important in the context of a midlife risk-reduction intervention for LOAD. For this study we assessed known LOAD risk factors (age, sex, and APOE4 genotype) in a transgenic mouse model with hAPOE alleles (JAX 27894 APOE3/3 KI and JAX #29018 APOE4/4 KI) bred to homozygous B6(SJL)-Apptmq.qAduci/J animals (JAX #030898, hAbeta-loxP-KI). hAPP hAPOE3/3 and hAPP hAPOE4/4 mice were exposed to midlife combinatorial therapy intervention at 15 month (human equivalent 49 years-old). Both male and female mice were orally treated with combination drug formulations or control via chow across a 30 or 90-day intervention period (human equivalent 51 years-old or 56 years-old, respectively). Animals were single housed and monitored weekly to determine accurate dosing. To assess the molecular mechanisms of midlife combinatorial therapeutic intervention in the context of AD risk, we conducted analyses of both plasma and the brain. Sex, APOE genotype, and combination-specific differences were identified in plasma levels of total cholesterol, HDL, LDL, and glucose. We found combination-specific differences in inflammatory profiles using 1) multi-color flow cytometry to measure lymphocytes (CD3, CD4, CD8b, CD69), monocytes (Ly-6C, CD43), and neutrophils (CD62L, CXCR4) in peripheral blood and meninges and 2) ELISA assays to quantify protein levels of β-Amyloid (Aβ) 40-42, and proinflammatory cytokine levels including TNF-α, IL-6, and IL-1β in plasma and cortex. Understanding the therapeutic potential of FDA-approved combinatorial precision intervention strategies warrants further investigation in LOAD. Strategies targeting both non-modifiable and modifiable risk factors demonstrate

promise toward the National Alzheimer's Project Act mission to prevent or effectively treat Alzheimer's disease and related dementias by 2025.

Disclosures: H. Van Rossum: None. **G. Torrandell:** None. **E. Reyes-Reyes:** None. **Y. Shang:** None. **R.D. Brinton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RDB is President of NeuTherapeutics, LLC.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.02/E38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG080773

Title: Modulation of ApoE by the mevalonate pathway and inflammation

Authors: *J. MILSTEIN, J. A. KULAS, S. HOSSEINIBARKOOIE, T. WEIGEL, H. A. FERRIS;
Univ. of Virginia, Charlottesville, VA

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease characterized by the aggregation of amyloid-β plaques and neurofibrillary tau tangles, and is often associated with neuroinflammation. The strongest genetic risk factor for developing AD is the ε4 allele of Apolipoprotein E (ApoE). ApoE is an integral component of HDL-like lipoparticles that are secreted by astrocytes under homeostatic conditions, and are also secreted by microglia in response to neuroinflammation like that observed during AD disease progression. These particles carry lipids and proteins, particularly cholesterol, and bind to LDL receptor related protein 1 (LRP1), leading to endocytosis of the particle and its contents. Previous work from our lab has shown astrocyte cholesterol synthesis through the mevalonate pathway is required for development of AD pathology in an AD mouse model. The mevalonate pathway is responsible for controlling two vital cellular processes, cholesterol production and protein prenylation. However, the roles that both the mevalonate pathway and inflammation play in regulating ApoE and whether they act in conjunction or separately in doing so is not well-understood. Here, we use pharmacological treatments of mouse mixed glial primary cultures to address these questions. We find that the mevalonate pathway has different effects on ApoE depending on which part of the pathway is being targeted pharmacologically. Specifically, inhibiting the protein prenylation arm of the pathway with either simvastatin or the prenylation inhibitor FGTI-2734 reduces secretion of ApoE, whereas inhibiting the cholesterol synthesis arm of the pathway with zaragozic acid reduces the size of the ApoE lipoparticles being secreted from the cells. In addition, we observe that treating our cultures with an established inflammatory cytokine cocktail inhibits ApoE secretion independently of protein prenylation. Interestingly, we find that

inhibiting protein prenylation reduces cellular levels of LRP1 and that treating cells with an LRP1 antagonist induces inflammatory activation of microglia, the latter result confirming previous reports. Overall, our data suggest that inflammation and protein prenylation regulate ApoE secretion through different mechanisms, and that cholesterol synthesis controls the generation of mature, large ApoE lipoparticles. Additionally, our data suggest involvement of LRP1 modulation by protein prenylation and inflammation in their effects on ApoE.

Disclosures: J. Milstein: None. **J.A. Kulas:** None. **S. Hosseinibarkooie:** None. **T. Weigel:** None. **H.A. Ferris:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.03/E39

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01 AG084485
Cure Alzheimer's Fund

Title: Longevity treatments affect Alzheimer's neuropathology in aged male EFAD mice

Authors: *A. CHRISTENSEN, A. ZAIDI, C. J. PIKE;
Davis Sch. of Gerontology, USC, Los Angeles, CA

Abstract: Aging is the greatest risk factor for Alzheimer’s disease (AD). The primary genetic risk factor for AD is the e4 allele of apolipoprotein E (*APOE4*). Interestingly, *APOE* genotype also regulates aging and longevity, with *APOE4* associated with decreased longevity in both humans and rodents. Several pathways impaired by normal aging and *APOE4* are implicated in AD pathogenesis, suggesting that interventions known to improve health- and lifespan by targeting age-related pathways may also function as effective therapeutic strategies for AD, especially in the context of *APOE4*. To investigate this topic, we studied the independent and combined efficacies of two longevity interventions in EFAD mice, a rodent model of AD with knock-in of human *APOE3* or *APOE4* and overexpression of familial AD transgenes. The first intervention was Fasting Mimicking Diet (FMD), a version of caloric restriction that reduces caloric intake for 4 consecutive days once every 14 days while maintaining the intake of micronutrients. The second intervention was 17α-estradiol (17αE2), a naturally occurring weak estrogen and stereoisomer of the primary estrogen 17β-estradiol, that has been shown to increase lifespan as well as beneficially regulate inflammatory and metabolic pathways. Sixteen-month-old male *APOE3* and *APOE4* EFAD mice were randomized into one of four treatment groups: (1) vehicle + *ad libitum* diet; (2) vehicle + FMD; (3) 17αE2 + *ad libitum* diet; or (4) 17αE2 + FMD. After nine weeks of treatment, outcomes on a range of systemic and neural were determined. Systemically, *APOE4* mice generally showed higher levels of age-related measures, which tended to be improved by 17αE2 and to a lesser extent by FMD. In brain, both 17αE2 and

FMD reduced AD-related measures (e.g., amyloid accumulation), but there was no additive benefit with combined treatment. These data show that both FMD and 17αE2 improved metabolic and neuropathological outcomes in aged EFAD mice, findings that support continued investigation of longevity-promoting interventions for improvement in late stages of AD.

Disclosures: A. Christensen: None. **A. Zaidi:** None. **C.J. Pike:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.04/E40

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG068395
Alzheimer's Drug Discovery Foundation

Title: Comparison of risk-modifying, Alzheimer's disease-associated APOE isoforms in lipid-bound state provides insight into structural differences

Authors: *R. TUCKEY[1], R. A. GREER[2], H. DEAN[3], E. D. ROBERSON[4], Y. SONG[2]; [1]Neurol., UAB Neurosci. Grad. Programs, Birmingham, AL; [2]Biomed. Engin., Univ. of Alabama at Birmingham, Birmingham, AL; [3]Biomed. Engin., [4]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Genetic variants in *APOE*, encoding the lipid carrier protein apolipoprotein E, are strongly associated with altering risk of developing Alzheimer's disease (AD), the leading cause of dementia worldwide. The common variants *APOE2* and *APOE4*, are associated with decreased and increased risk of developing AD, respectively, relative to the most common *APOE* variant, *APOE3*. The rare *APOE* variants *APOE3-R136S* (Christchurch), *APOE3-V236E* (Jacksonville), and *APOE4-R251G* have been found to protect against AD. Previously, we examined how these variants altered APOE structure in its lipid-free state. These models are limited as APOE is mostly in a lipid-bound state *in vivo*. Our current study uses molecular dynamics (MD) simulations to examine how common and rare variants in *APOE* alter its interaction with lipids while also comparing lipid-free and lipid-bound structures. Our starting APOE structure, provided by Prakashchand *et al.*, was generated from coarse-grained MD simulations of a mutant APOE structure (PDBID: 2L7B) in the presence of DPPC lipid molecules. We then took the lipid-bound APOE mutant and converted it to APOE3. Subsequent simulations were used to generate a representative structure of APOE3 before mutating it to the other APOE isoforms. These were made using APOE3 as it can be converted to all other variants via a single amino acid substitution using PyMOL, except for APOE4-R251G which was made using APOE4. MD simulations for each APOE variant were performed in triplicate beginning with separate starting APOE3 molecules. The last 300 ns of equilibrated simulations for each simulated system were used for analysis. Simulations of the APOE-lipid complex allowed for

analysis of each isoform in relation to their lipid interactions, conformational stability, secondary structure occupancy, dynamic cross-correlated motion, and solvent accessible surface area. Findings from this study identify features that distinguish rare isoforms from common isoforms and show effects of lipidation on each APOE isoform. Comparison of isoforms by their lipid interactions, conformational stability, secondary structure occupancy, dynamic cross-correlated motion, and solvent accessible surface area highlight the impact variants have on APOE-lipid interactions. Alterations in structure and lipid binding ability of rare isoforms could potentially change downstream function, thereby contributing to their protection against developing AD. This work was supported by the NIH R01AG068395 and Alzheimer's Drug Discovery Foundation.

Disclosures: R. Tuckey: None. **R.A. Greer:** None. **H. Dean:** None. **E.D. Roberson:** F. Consulting Fees (e.g., advisory boards); AGTC, Lilly, Genentech. Other; Editorial Board for Journal of Neuroscience. **Y. Song:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01DK121497
NIA Grant T32AG078114
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Margaret "Peg" McLaughlin and Lydia A. Walker Fund

Title: Exploring the influence of APOE polymorphisms on neuronal and hepatic mitochondrial bioenergetics and dynamics

Authors: *C. LYSAKER, C. JOHNSON, V. CSIKOS DRUMMOND, E. FRANCZAK, X. CAO, R. KEMNA, C. S. MCCOIN, J. P. THYFAULT, P. C. GEIGER, J. K. MORRIS, H. M. WILKINS;
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Abstract: Background: Emerging evidence has shown that liver dysfunction is closely associated with Alzheimer's disease (AD) risk, suggesting the liver is a novel target for the study of AD. Variation in the apolipoprotein E (*APOE*) gene not only influences the risk of AD, but other diseases as well. While APOE is secreted by both the liver and brain, it does not readily cross the blood brain barrier (BBB) resulting in two distinct pools of APOE. Additionally, APOE has roles in physiological and metabolic processes such as lipid transport, as well as amyloid beta clearance from the brain, but its direct effect on mitochondrial function is not well characterized. We look to investigate the role of different APOE isoforms on mitochondrial function, and further elucidate how these genetic variations impact liver and brain health.

Despite what is known regarding APOE, the full extent of its impacts on liver and brain health in relation to mitochondrial function is not well understood. **Methods:** In this preliminary study, we used male and female APOE targeted replacement mice on a C57BL/6N background (Taconic Biosciences), homozygous for either *ε3* or *ε4* alleles and aged to 16 weeks on a standard chow diet. Both liver and brain tissue were collected upon euthanasia with measures of mitochondrial function assessed using Seahorse XF analysis and Oroboros O2k respirometry. Proteomics analysis was conducted on isolated mitochondria from both tissues and confirmed using western blot analysis. **Results:** We found that male and female APOE4 mice have reduced carbohydrate driven mitochondrial respiration in the liver, but not the brain when compared to their APOE3 counterparts. Additionally, male APOE4 mice showed reduced state 3S and uncoupled lipid driven respiration in the liver when compared to APOE3 male mice. Pathway analysis revealed that APOE4 mice had enriched expression of proteins associated with sirtuin signaling, EIF2 signaling, and reduced oxidative phosphorylation in the liver. In the brain, the mevalonate pathway and NAD signaling were increased in APOE4 mice when compared to APOE3 mice. Additionally, DRP1 and MFN2, proteins associated with mitochondrial fission and fusion, showed differential expression by both genotype and tissue when compared in the liver and brain. **Conclusions:** Our data show early APOE genotype-dependent changes to mitochondrial bioenergetics occurring in both the liver and brain as well as suggested alterations in mitochondrial dynamics. Further studies are ongoing to investigate mechanistic changes that underlie these differences in metabolism, and their implication of the liver and brain function.

Disclosures: C. Lysaker: None. **C. Johnson:** None. **V. Csikos Drummond:** None. **E. Franczak:** None. **X. Cao:** None. **R. Kemna:** None. **C.S. McCoin:** None. **J.P. Thyfault:** None. **P.C. Geiger:** None. **J.K. Morris:** None. **H.M. Wilkins:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.06/F1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH-NIGMS: 5P20GM103446
NIH: 5R25GM122722-04
TMCF | Novartis Fellowship

Title: Overexpression of heat shock protein 27 modulates hippocampal apolipoprotein E and reduces aggregation of transactive response DNA binding protein 43

Authors: *M. ABEER, A. GAUFF, J. SHERAD, I. BROOKS, M. GITCHO;
Delaware State Univ., Dover, DE

Abstract: Aggregation of transactive response DNA binding protein 43 (TDP-43) is the primary pathological feature of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).

Recently, in up to 50% of Alzheimer's disease (AD) cases, TDP-43 pathology was discovered and this pathology has been referred to as limbic-predominant age-related TDP43 encephalopathy (LATE). Several studies reported that TDP-43 binds to heat shock protein family B (small) member 1 (HSPB1 or HSP27) but no functional evaluation of this interaction has been explored. Inducing expression of HSP27 has been shown to be protective of many other disease conditions and has been shown to reduce aggregation of amyloid in AD. In general, the goal is to utilize both primary neuronal cultures and mice that are selectively expressing pathogenic TDP-43, HSP27, and apolipoprotein E (APOE) in the brain to characterize the effect of HSP27 overexpression on TDP-43 and APOE. This will give us a better model to understand TDP-43 proteinopathies. In the present study, we hypothesize that increased expression of HSP27 may reduce TDP-43 aggregation and alter mitochondrial morphology. A new transgenic mouse model was developed to selectively drive human HSP27 and pathological TDP-43 with a defective nuclear localization signal (ΔNLS) in the hippocampus and neocortex using the Ca^{2+}/calmodulin protein kinase (Camk2a) tetracycline-inducible system. The following genotypes have been evaluated for immunohistochemistry, biochemistry (solubility fractionation), and Western blot: wild-type, Camk2a/ΔNLS, Camk2a/HSP27 and Camk2a/HSP27/TDP43ΔNLS at 4 months of age. Preliminary *in vitro* results show that cells overexpressing HSP27 reduce aggregation and protein levels of TDP43. However, mice overexpressing HSP27 in a TDP43ΔNLS background in the hippocampus and cortex do not show any reduction in the soluble fraction. Interestingly, increased expression of HSP27 in the hippocampus of Camk2a/HSP27 mice showed a significant reduction of endogenous APOE expression. Immunohistochemical and bioenergetic experiments are currently being carried out to evaluate the brain and mitochondrial morphology upon HSP27 overexpression. Overall, our initial data suggests that modifying HSP27 expression modulates endogenous APOE levels.

Disclosures: **M. Abeer:** None. **A. Gauff:** None. **J. Sherad:** None. **I. Brooks:** None. **M. Gitcho:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.07/F2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG047644
JPB

Title: Utilizing a cell culture based novel cellular thermal shift assay to understand the structure and function relationship of ApoE variants.

Authors: ***R. J. JACKSON**[1,2], S. DIERKSMEIER[1,3], J. C. MELTZER[1], J. COOPER[4], Z. FAN[1], E. SERGIENKO[7], S. OLSON[7], D. STRICKLAND[4,5,6], M. R. JACKSON[7], B. T. HYMAN, MD,PhD[1,2];

[1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Dept. of Neurol., Harvard Med. Sch., Boston, MA; [3]Univ. of Oxford, Oxford, United Kingdom; [4]The Ctr. for Vascular and Inflammatory Dis., [5]Departments of Physiol., [6]Departments of Surgery, Univ. of Maryland Sch. of Med., Baltimore, MD; [7]Conrad Prebys Ctr. for Chem. Genomics, Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: Dementia and more specifically Alzheimer's Disease (AD) currently pose a global health crisis with more than 3 million cases of AD in the US alone. Inheritance of the ε4 allele of apolipoprotein E (ApoE) is the strongest genetic risk factor associated with the sporadic form of AD, whereas the rare ApoE ε2 allele has the opposite effect. ApoE4 differs from ApoE3 by a single amino acid, an arginine instead of cysteine at position 112. This small change presumably alters the conformation of the protein, altering its activity in many biological pathways resulting in both gain and loss of function activities that increase the risk for AD. We and others have previously shown that purified recombinant ApoE4 has a lower thermal stability than that of ApoE3 and that this change in thermal stability is indictive of a change in structure that is likely important for ApoE's function. To explore if this feature extends to ApoE protein in a cellular context we deployed a Cellular Thermal Shift Assay (CETSA), which measures the thermal stability (ie. melting point) of proteins in complex and native cell states rather than using purified protein. We found that ApoE4 denatures at a lower temperature than ApoE3 in brain extract from both human cases and mouse models.

To further study this phenomenon we have developed a system that uses a HiBiT-LgBiT (Promega) split luciferase. This system consists of a small, 11 amino acid peptide tag, HiBiT, and its complementary partner LargeBiT. These proteins bind with high affinity and perform with excellent sensitivity and linear dynamic range. We have transfected HEK cells with plasmids encoding for HiBiT tagged ApoE of multiple isoforms and found that the different melting points between ApoE 2, 3 and 4 were maintained in this system. We then went on to use this cell culture model to investigate the effect of rare variants of ApoE that have been implicated in disease including R136S, R145C, L28P, V236E, and R251G. We have found that some of these single amino acid changes have significant effects on the thermal stability of ApoE indicating that these changes in structure are likely having a functional impact.

We then went on to further understand the structure and function relationship of ApoE mutants. This work shows that thermal stability in this assay is a good surrogate for protein structural changes that have real world implications in terms of relative risk for generating AD and that investigating ApoE structure and function is crucial to our understanding of this important risk factor.

Disclosures: R.J. Jackson: None. **S. Dierksmeier:** None. **J.C. Meltzer:** None. **J. Cooper:** None. **Z. Fan:** None. **E. Sergienko:** None. **S. Olson:** None. **D. Strickland:** None. **M.R. Jackson:** None. **B.T. Hyman:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.08/F3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSFC82104415
NSFC31872311

Title: Ameliorating effects of GSK2606414 in ApoE4 accelerated endoplasmic reticulum stress and cognitive impairments, a mice study

Authors: *X. LONG[1], Y. YANG[1], L. DU[2], X. XIE[1];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative condition that results in dementia among a population of over 50 million elderly individuals. Apolipoprotein E4 (ApoE4) allele is a robust genetic risk factor for AD, conferring a higher risk compared to the more common ApoE3 allele. AD is characterized by the decline in memory that is induced by neuronal endoplasmic reticulum (ER) stress and unfolded protein responses (UPR), which are further enhanced by PERK activation. GSK2606414 is a PERK inhibitor that was initially identified as a UPR modulator with anticancer and antiproliferative properties. The neuropharmacological effects of GSK2606414 have not been extensively studied on any ApoE-related AD animal model. This study aims to investigate the effects of GSK2606414 on PERK inhibition in APOE4 knock-in mice. We compared the AD progression between ApoE3 and ApoE4 knock-in mice, including beta-amyloid pathology, long-term spatial learning, and cognitive functions. GSK2606414 suppressed protein expressions in the PERK-eIF2α pathway and exhibited improvements in cognitive performance. The study also addressed the alleviating effects of GSK2606414 on AD-related ER stress and memory decline. These findings indicate the pharmacological effects of GSK2606414 on ApoE4-associated AD pathology and suggest future directions for ApoE-targeted treatments.

Disclosures: **X. Long:** None. **Y. Yang:** None. **L. Du:** None. **X. Xie:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.09/F4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The isoform-dependent effects of apolipoprotein E on the deposition of Aβ

Authors: *M. TANAKA[1], A. KOKAWA[2], H. UCHIGAMI[3], T. HASHIMOTO[4], T. IWATSUBO[5];
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Abstract: The *APOE ε4* allele is a strong genetic risk factor for the development of Alzheimer's disease (AD). To investigate the role of apoE in the pathogenesis of AD, we crossed APP transgenic (tg) mice with human *APOE3* knock-in (KI) mice, and found that APP tg/*APOE3* KI mice exhibited significantly lower Aβ deposits compared to APP tg mice, suggesting that human apoE3 may suppress the deposition of Aβ. To test this hypothesis, we performed an *in vivo* seeding experiment that allows the induction of Aβ deposition in the brain by a single inoculation of Aβ seeds. Hippocampal inoculation of TBS-soluble fraction from brains of Aβ-laden APP tg mice induced deposition of Aβalong the molecular layer of the dentate gyrus in the hippocampus of APP tg mice. Notably, both APP tg/*APOE3* KI and APP tg/*APOE4* KI mice exhibited significantly less Aβ deposition than APP tg mice. In addition, seed-induced Aβ deposition was significantly higher in APP tg/*APOE4* KI mice than in APP tg/*APOE3* KI mice. These data suggest that apoE affects Aβ deposition in an isoform-dependent manner.To further elucidate the role of apoE on the deposition of Aβ, we performed an *in vivo* seeding experiment in apoE-deficient APP tg (APP tg / APOE KO) mice. We found that no seed-induced Aβ deposition was observed in the hippocampus of APP tg/APOE KO mice. Adeno-associated virus-mediated astrocyte overexpression of human apoE3 resulted in the induction of Aβ deposits in the hippocampus of APP tg/APOE KO mice. These data suggest that apoE is an essential factor for seed-dependent Aβ deposition. Taken together, our findings implicate that apoE modulates Aβ deposition in an isoform-dependent manner by facilitating the seeding activity of Aβ seeds in the brain.

Disclosures: **M. Tanaka:** None. **A. Kokawa:** None. **H. Uchigami:** None. **T. Hashimoto:** None. **T. Iwatsubo:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.10/F5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: US National Institute of Neurological Disorders and Stroke
UH3 NS100121
RF1 NS110048
Good Ventures
Open Philanthropy

Title: Deciphering ApoE Christchurch protein-protein interactions in the brain

Authors: ***P. A. PEREZ**[1], C. MARINO[1], C. ORTIZ[2], S. WANG[3], Y. T. QUIROZ[4], J. ARBOLEDA-VELASQUEZ[1];

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Abstract: Our group previously identified an individual who despite carrying the *PSEN1* E280A mutation leading to early-onset dementia, only developed cognitive impairment three decades after the family's expected age of onset. We found that she was homozygous for a rare mutation in *APOE,* called Christchurch (R136S, APOE3Ch), and that this mutation appears to have protected her against tau pathology. While a mechanism of protection has been proposed based on the protein interactions between the mutated region of ApoE and Heparan sulfate proteoglycan (HSPG), a comprehensive understanding of other ApoECh protein-protein interactions in the brain is still unknown. To address this, we performed affinity purification experiments using His-tagged ApoE3 and ApoE4 (wildtype and Christchurch) proteins produced in HEK cells. Our goal was to bait potential interacting partners from adult mice brain protein lysates (n=3). We identified the interactors via mass spectrometry and quantified the number of proteins bound to ApoE wild type (ApoEwt) and ApoECh. Additionally, we performed an analysis based on the abundance of the proteins using the Ingenuity Pathway Analysis software (IPA). Our results revealed a lower number of proteins interacting with ApoE4wt compared to ApoE3wt. ApoE4Ch showed a trend towards an increase in the number of interactors compared to ApoE4wt (P=0.08). Notably, Mapt protein (Tau) was one of the upstream regulators in the IPA analysis, exhibiting a stronger bound to ApoE3Ch and ApoE4Ch compared to the wild type counterparts. To validate this finding, we performed a pull-down assay using recombinant human Tau-441 protein 2N4R with the His-tagged ApoE proteins used previously, confirming a higher affinity of human Tau protein to ApoE3Ch and ApoE4Ch compared to the wild type proteins. In this study, we identified the different ApoECh interacting partners and validated Tau as an interacting partner that is affected by the presence of Christchurch mutation.

Disclosures: P.A. Perez: None. **C. Marino:** None. **C. Ortiz:** None. **S. Wang:** None. **Y.T. Quiroz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor of a patent filed by Mass General Brigham to leverage therapeutics inspired by the Christchurch findings. **J. Arboleda-Velasquez:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventors on a patent filed by Mass General Brigham to leverage therapeutics inspired by the Christchurch findings, Co-founder of Epoch Biotech, an LLC developing resilient case-inspired therapeutics.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.11/F6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH AG

Title: Apoe Isoforms Differentially Modulate Tau Propagation in Regions Associated with Early Alzheimer's Disease in a Novel Mouse Model

Authors: *H. A. ARAIN, T. NURIEL;
Taub Institute; Columbia Univ. Med. Ctr., New York, NY

Abstract: Possession of the APOE4 allele is the strongest risk factor for developing the sporadic form of Alzheimer's disease (AD). Extensive research in the field has largely focused on the roles APOE has on modulating amyloid-beta (abeta) pathogenesis. Recently, studies have shifted to elucidating the role APOE plays in tau pathology. However, it remains unclear if differential APOE isoform expression can modulate pathological tau propagation in regions associated with early tau accumulation in AD. To investigate the role APOE plays in the propagation of tau in AD-vulnerable brain regions, we created a novel APOE-expressing mouse model that mimics tau pathology observed early on in AD. To facilitate the expression of tau mainly in the entorhinal cortex, mice expressing human MAPT harboring the P301L mutation, under control the neuropsin-tTa promoter, were crossed to humanized homozygous APOE3/3 or APOE4/4 target-replacement mice. Both male and female mice were analyzed at middle and old age (15-17 and 25-27 months, respectively) by Morris Water Maze and structural MRI. Mice were subsequently euthanized, and neuropathological analysis was performed for overt tau pathology. MRI and histological analysis of the middle-aged and old entorhinal cortex and hippocampus demonstrates differential tau propagation and atrophy that is affected by APOE genotype. Interestingly, our results point mainly to decreased tau spread in APOE4-expressing mice. Upon analysis of the middle-aged mice, separated by sex, we have discerned a significant decrease in tau propagation to the hippocampus (CA1, CA3; $p<0.01$) and lateral entorhinal cortex ($p<0.01$) in female mice containing the APOE4/4 allele compared to female APOE3/3 mice. This effect in tau spread was attenuated in both male APOE3/3 and APOE4/4 mice. Here we report for the first time the generation of a novel APOE-tau mouse model that recapitulates the region-specific tau pathogenesis observed in early AD, independent of abeta pathology. Our results offer novel insights into APOE's role in modulating the propagation of tau along anatomically connected, vulnerable AD brain regions.

Disclosures: H.A. Arain: None. **T. Nuriel:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.12/F7

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: In vitro Model of Alzheimer’s Disease based on Neurons and Astrocytes Generated from Patient iPSCs using Transcription Factor-Based Rapid Differentiation Technology

Authors: *R. TANAKA[1], T. SAMESHIMA[1], R. YAMOTO[1], T. TANAKA[2], M. SEO[2], T. HOSOYA[1];
[1]Ricoh Company, Ltd., Kawasaki-shi, Kanagawa, Japan; [2]Elixirgen Scientific Inc., Baltimore, MD

Abstract: Alzheimer's disease (AD) is the most common form of dementia. Since no animal models fully recapitulate the AD phenotype and drug responses, human iPS cell-derived cells are a highly valuable tool in the investigation of the AD pathology. The major pathological phenotypes of AD are extracellular accumulation of amyloid plaques and intracellular neurofibrillary tangles of phosphorylated Tau. Accumulation of Aβ and/or phosphorylated Tau has been observed in neurons generated from patient iPSCs. In this study, we asked whether the pathological phenotypes can be observed in patient iPSC-derived neurons and astrocytes generated by the transcription factor-based technology for rapid differentiation (Quick-Neuron™). iPSC-derived neurons generated from a sporadic Alzheimer's disease patient with a genetic polymorphism in the APOE4 gene (AD neurons) were cultured for one to eight weeks, with neuros from a healthy donor as control. After six weeks of culture, the AD neurons exhibited significantly higher accumulation of Aβ40 and Aβ42 in the culture media compared to the control neurons. Tau accumulation and Tau phosphorylation were also significantly higher in the AD neurons after four weeks culture. β-secretase inhibitors that inhibit Aβ production significantly reduced the accumulation of Aβ40 and Aβ42 in the AD neurons. These results imply that the patient-derived Quick-Neuron™ exhibit the pathological phenotypes of Alzheimer's disease within four to six weeks of culture. Because astrocytes play a central role in APOE4 mediated cholesterol transport to neurons, we are also investigating the phenotypes of astrocytes generated from the patient iPSC using the rapid differentiation technology (Quick-Glia™). Contribution of the neurons and astrocytes generated from AD patients using the rapid differentiation technology will be discussed in the context of the disease mechanism investigation and phenotypic drug screening.

Disclosures: **R. Tanaka:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **T. Sameshima:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **R. Yamoto:** A. Employment/Salary (full or part-time):; Ricoh Company, Ltd. **T. Tanaka:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **M. Seo:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **T. Hosoya:** A. Employment/Salary (full or part-time):; Toshihiko.Hosoya@jp.ricoh.com.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.13/F8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01EY027779
NIH Grant R01EY027779-Supplement

NIH Grant R01EY032080
Research to Prevent Blindness

Title: Retinal Phenotyping of the APOE4 Knock-In Mouse Model of Alzheimer's Disease under Hyperglycemia

Authors: *G. D. HARTMAN, S. D. ABHYANKAR, Q. LUO, T. W. CORSON, A. L. OBLAK, B. T. LAMB, A. D. BHATWADEKAR;
Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease characterized by cognitive decline. There is an unmet need to identify new biomarkers to aid with diagnosis. Retinal phenotypes are promising biomarkers for AD, as AD patients have several ocular abnormalities. Late-onset AD (LOAD) accounts for 95% of AD cases, with the apolipoprotein ε4 allele (*APOE4*) being the strongest genetic risk factor. Those with diabetes and the *APOE4* allele may have worsened retinal function and accelerated development of diabetic retinopathy (DR). Although the *APOE4*-knock-in (*APOE4*-KI) mouse model is available, the retinal phenotype is unknown. We assessed the retinal structure and neural function of LOAD-risk mice (*APOE4*-KI) compared to LOAD-neutral mice (*APOE3*-KI) and whether a diabetogenic Western diet (WD) accelerates the development of the phenotype. During a 6-month period, male and female mice carrying the *APOE4* and *APOE3* genetic variants were subjected to either Western diet (WD) or control diet (CD). Body weight and fasting blood glucose levels were monitored. Retina structure was evaluated using fundus examination and optical coherence tomography. Vascular architecture was visualized with fluorescein angiography. Neural function of the retinas was assessed using an electroretinogram (ERG). Both *APOE3*- and *APOE4*-KI mice on WD exhibited increased body weight and fasting glucose compared to CD. Retinal thickness was increased in *APOE4*-KI WD compared to *APOE4*-KI CD. Arterial tortuosity was increased with *APOE4*-KI on WD compared to APOE3-KI on WD. *APOE4*-KI mice exhibited reduced a-wave and b-wave amplitudes compared to *APOE3*-KI mice. WD further exacerbated these reductions. LOAD-risk mice exhibit heightened vascular dysfunction compared to LOAD-neutral mice. The introduction of a high-fat WD further aggravated a range of ocular irregularities, implying that the combination of *APOE4* and diabetes might expedite retinal dysfunction. The reduced ERG response observed in LOAD-risk mice signifies compromised neural activity in photoreceptors, on-bipolar cells, and Müller cells. These discoveries shed light on the mechanisms behind retinal dysfunction in a mouse model with a heightened risk of LOAD combined with diabetes and identifies potential novel biomarkers for AD.

Disclosures: G.D. Hartman: None. **S.D. Abhyankar:** None. **Q. Luo:** None. **T.W. Corson:** None. **A.L. Oblak:** None. **B.T. Lamb:** None. **A.D. Bhatwadekar:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.14/G1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG076235

Title: Effects of Adiponectin Signaling on lipid homeostasis in astrocytes

Authors: *J. M. NOUGAISSE, Y. LEI, X.-Y. LU;
Neurosci. & Regenerative Med., Augusta Univ., Augusta, GA

Abstract: Disruptions in lipid homeostasis have been implicated in various neurological disorders and neurodegenerative diseases, including Alzheimer's disease (AD). However, the specific contributions of lipid dyshomeostasis to the pathology of AD and the underlying mechanisms require further investigation. Among the apolipoproteins involved in brain cholesterol transport, ApoE plays a significant role as a major component of high-density lipoprotein (HDL)-like particles secreted by astrocytes. The ApoE4 isoform is the most prevalent genetic risk factor for late-onset AD. ApoE in the brain is primarily expressed by astrocytes and microglia. Astrocytes expressing ApoE4 exhibit increased intracellular accumulation, as indicated by a higher number of lipid droplets, compared to astrocytes expressing ApoE2 and ApoE3. Adiponectin, an adipokine known to enhance HDL biogenesis and secretion in peripheral tissues, can cross the blood-brain barrier. We hypothesized that adiponectin is involved in regulating cholesterol synthesis and secretion in astrocytes. To test this hypothesis, we treated astrocytes expressing ApoE2, ApoE3, and ApoE4 with adiponectin and analyzed intracellular and extracellular lipid levels. Our findings suggest that adiponectin signaling contributes to astrocyte lipid homeostasis. Future studies will explore the underlying mechanisms that mediate the effects of adiponectin in vitro and in vivo.

Disclosures: J.M. Nougaisse: None. **Y. Lei:** None. **X. Lu:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.15/G2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R21AG066496-01
NIH Grant 1F31AG082498-01
Kleberg and Semmes Foundation Grant

Title: Assessing the pathogenic role of Alzheimer’s disease genetic risk factor ApoE4 in 3D cortical organoids

Authors: *K. K. MEYER-ACOSTA, A. ARUK, A. MUNIZ PEREZ, Y. RAFATI, J. HSIEH;
Neuroscience, Developmental, and Regenerative Biol., Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Alzheimer's disease (AD) is substantially heritable with genetic risk factors significantly contributing to AD risk. The leading genetic risk factor for AD, Apolipoprotein E4 (APOE4), is associated with a 3-12 fold increased risk for AD. AD develops decades prior to cognitive decline, and studying the earliest pathogenic mechanisms that precede end-stage AD pathology is technically challenging. Human induced pluripotent stem cell (iPSC) technology provides a tool to study genetic effects on human disease-relevant phenotypes, in a variety of cell-types. There is considerable evidence that GABAergic neurons, the primary inhibitory neuronal subtype in the brain, are disproportionately susceptible with APOE4 genotype in vivo, and in vitro; In a study using iPSC derived cultured neurons, APOE4/4 results in loss or degeneration of GABAergic neurons. Patient-specific iPSC-derived cortical organoids can provide a snapshot of early APOE4 mediated pathogenic mechanisms that precede end stage pathology and later AD-related pathology. To study the cell-type specific effects of APOE4, we have generated two types of iPSC-derived cortical organoids, human cortical organoids (hCO) enriched in excitatory neurons, and human subpallial organoids (hSO) enriched in inhibitory neurons. We have preliminary data suggesting the APOE4 allele alters APOE expression, growth, and related cellular phenotypes compared to organoids carrying the non-risk allele, APOE3. These preliminary findings support the notion that APOE4 may influence neuronal subtypes differentially leading to increased AD-risk.

Disclosures: K.K. Meyer-Acosta: None. **A. Muniz Perez:** None. **Y. Rafati:** None. **J. Hsieh:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.16/G3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIMH Award R56MH125655

Title: Preliminary behavioral studies suggest phenotypic differences between humanized ApoE4 knock&-in and humanized ApoE3 knock&-in rats

Authors: N. RIVEIRA, D. OKWUBODU, ***J. TARANATH**, L. LEE COLGIN;
Univ. of Texas at Austin, Austin, TX

Abstract: Apolipoprotein-E4 (ApoE4) is the highest genetic risk factor for late-onset Alzheimer's disease in humans. We performed behavioral assays with humanized-ApoE4 knock-in (hApoE4-KI) rats and humanized-ApoE3 knock-in (hApoE3-KI) rats as controls. In pilot behavioral studies, hApoE4-KI (n=5) and hApoE3-KI (n=6) rats ran on a one-dimensional circular track, performed an object-place-association (OPA) memory task (as previously described in *Zheng et al. 2016*), and were tested for anxiety in an open field arena. The rats ran on the circular track for three 10-minute sessions with 10-minute inter-session rest periods across

4 days. Putative head scanning events were identified with an algorithm used previously in *Monaco et al. 2014*. We observed preliminary evidence of increased head scanning event durations per session in hApoE4-KI rats compared to hApoE3-KI rats. Also, the head scanning event rate (head scanning events per total session pause times) was higher in hApoE4-KI rats compared to hApoE3-KI rats. During the OPA task, two identical objects were placed at adjacent corners of an open-field arena during an initial familiarization session. During a subsequent novel stimulus session, one of the two identical objects was placed in a different location (NL condition) or was replaced with a different object either in the same location (NO condition), or in a different location (NO + NL condition). In preliminary data, we observed that hApoE4-KI rats spent less time near the new object and locations in the NO and NL sessions compared to hApoE3-KI rats, potentially indicating decreased novelty recognition. Further, both groups showed similar exploratory behaviors in open-field arenas. Overall, these results suggest disturbances in exploratory behaviors of hApoE4-KI rats that may inform future studies of Alzheimer's disease.

Disclosures: **N. Riveira:** None. **D. Okwubodu:** None. **J. Taranath:** None. **L. Lee Colgin:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.17/G4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Society DTC (CD)
Sussex Neuroscience PhD studentship (ACS)
Alzheimer's Research UK South Coast Network grant (ACS & SLK)

Title: Apolipoprotein E genotype effects on attention, everyday memory and brain activity

Authors: A. C. STUART, C. DEMIRBATIR, ***S. L. KING**;
Univ. of Sussex, Brighton, United Kingdom

Abstract: Carrying the APOE4 variant of the Apolipoprotein E gene increases the risk of late-onset Alzheimer's disease, faster age-related cognitive decline, and drives dysfunction in multiple cellular pathways. How APOE4 deficits in cognition develop across the lifespan are unknown, and in early life APOE4 may be cognitively beneficial. Separate cohorts of APOE3 and APOE4 targeted replacement mice (APOE-TR, female and male) were repeat-tested in either a five choice serial reaction time task (5CSRTT) or a new rapid everyday memory task across the lifespan. A third experiment measured activation of cFos in three and twelve month-old mice. The experiments sought to map the impact of APOE genotype on profiles of cognition and brain activation across their life span. APOE-TR mice demonstrated a complex set of genotype, age, and sex-dependent effects across all three experiments. We used a modified 5CSRTT task, where

mice have continuous access to the testing chamber and testing occurs 24 hours a day. We found response accuracy (correct / (correct + incorrect trials)) varied with stimulus duration (a measure of attention) but not sex, genotype or age. Some aspects of performance improved with age (likely due to repeat training), however, this also did not vary with genotype. To measure everyday memory we developed a new appetitive adapted Barnes maze to test rapid learning in a delayed match to place paradigm. We saw some differences between sex and genotype, though these varied across age and measure, with no obvious pattern. cFos immunoreactivity was measure in cohorts of three and twelve month old mice in response to a novel context. Three month APOE4-TR mice showed a larger ensemble of cFos+ neurons in CA1 compared with APOE3-TR mice. This response was modified by sex but not associated with dendritic structural differences in cFos+/cFos- neurons. The genotype difference was no longer significant at 12 months.Together our results suggest that there is very little difference in the cognitive profile of APOE3 and APOE4-TR mice in the context of repeat testing across the lifespan. However, we saw a state of hippocampal hyperactivity in APOE4-TR mice early in life. We hypothesise that repeat testing might provide an enrichment-induced protection from the predicted APOE4-driven neurocognitive decline. Future testing in age-matched naïve mice or combining genotype with an environmental insult (e.g. early life stress or inflammation) might reveal age-related APOE4 deficits in performance.

Disclosures: **A.C. Stuart:** None. **C. Demirbatir:** None. **S.L. King:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.18/G5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 1R01AG084472 - 01

Title: Rescue of ApoE4 related lysosomal autophagic failure by targeted small molecules: A multifaceted drug-discovery approach

Authors: *S. GRIFFIN[1], M. BALASUBRAMANIAM[2];
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Abstract: Introduction: Inheritance of the ε4 variant of the Apolipoprotein gene (*APOE*ε4) is the most impactful factor, genetic or otherwise, in the development of Alzheimer's disease (AD). We found a novel mechanistic explanation in the ability of this allele's protein product, ApoE4, to enter the nucleus, bind to the Coordinated Lysosomal Expression and Activity and Regulation DNA motif (CLEAR) and in this way repress transcription of three mRNAs essential to lysosomal autophagy (*SQSTM1*, *LAMP2*, and *MAP1LC3B*) in brain tissue from Alzheimer patient carriers of *APOEε4,4*, but not *APOE*ε3,3, thus prompting us to: *i*) identify and ii) directly target the ApoE4-CLEAR DNA-binding site with small molecules that we show restored

lysosomal autophagic clearance in cell and animal models of AD carrying human *APOEε4*. **Methods:** ApoE4 protein was assessed via multi-scale computational modeling for the presence of a stable druggable pocket. ApoE4-specific lead molecules were predicted using High-throughput Virtual Screening of a small-molecule library. Autophagic gene expression was assessed: *i*) in a glioblastoma cell line (T98G) expressing either ApoE3 or ApoE4; *ii*) in mouse primary astrocytes derived from an ApoE4 Targeted-Replacement mouse strain; and *iii*) in *C. elegans* models with pan-neuronal expression of human amyloid β-peptide (Aβ) accompanied by global expression of either human ApoE3 or ApoE4 protein. **Results:** Computational modeling predicted a novel druggable site in the ApoE4 protein that comprises its CLEAR DNA-binding region. High-throughput Virtual Screening predicted small molecules with high affinity for this binding site in the ApoE4 protein. Experimental characterization of the five top molecules identified a novel lead candidate that blocked interactions between ApoE4 and CLEAR DNA motifs in multiple *in vitro* model systems, restoring the expression of three TFEB-regulated mRNA transcripts (*SQSTM1, LAMP2,* and *MAP1LC3B*) in these models. Treatment with our predicted lead molecules also inhibited Aβ accumulation in a *C. elegans* line expressing ApoE4. **Conclusion:** Our identification of both the CLEAR DNA-interacting ligand-binding pocket in ApoE4 and small molecules that binds exclusively to this druggable pocket holds promise of restoring lysosomal autophagy in individuals who inherit one or both *APOEε*4 alleles. We have thus implicated a drug as a preventative agent to delay or prevent AD in the 50-65% of the AD population that carries at least one *APOEε*4 allele.

Disclosures: S. Griffin: None. **M. Balasubramaniam:** None.

Poster

PSTR258. ApoE and Associated Pathways I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.19/G7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG061114
R61NS114353
R01MH086507

Title: Endothelial cell APOE3 is an important regulator of neural function

Authors: *F. M. MAROTTOLI, H. ZHANG, E. FLORES-BARRERA, E. ARTUR DE LA VILLARMOIS, K. TSENG, L. M. TAI;
Anat. and Cell Biol., Univ. of Illinois At Chicago, Chicago, IL

Abstract: Human *APOE* is intricately involved in numerous aspects of neural function. Indeed, studies on aging and neurodegenerative disease have demonstrated greater cognitive decline during aging, poorer outcomes following stroke and traumatic brain injury, and higher risk of developing Alzheimer's disease with *APOE4* when compared to *APOE3*. *APOE* modulates

various functions throughout the body and increasing evidence emphasizes the impact of *APOE* on neurovascular function. Further, deficits in permeability, vessel coverage and cerebral blood flow are lower with *APOE3* compared to *APOE4* in aging and neurodegeneration in both humans and mouse models. It is, therefore, necessary to identify neurovascular functions modulated by *APOE3* to elucidate its impact on neurological functions. Brain endothelial cells are the highly specialized foundation of the neurovasculature and are responsible for its unique properties compared to other vascular systems. Currently, the role of endothelial cell *APOE3* in neurovascular function remains unresolved, and much of what is known about *APOE* and its role in the neurovasculature focuses on apolipoprotein produced by non-endothelial cells. However, we recently found that brain endothelial cell *APOE3* plays a protective role in neurovascular cell function *in vitro*. In the present study, we sought to advance these findings *in vivo* by testing whether the loss of endothelial cell *APOE3* is sufficient to impact brain vascular and neural function. We achieved this by evaluating brain function in a mouse model of humanized *APOE* at 9 months of age in which we induced the endothelial-specific knockdown of *APOE3*. In doing so, we found that the loss of endothelial cell *APOE3* results in disrupted neurovascular, neuronal, and behavioral function. Specifically, mice lacking endothelial cell *APOE3* have higher neurovascular permeability and lower vessel coverage, deficits in spatial memory and fear memory extinction, and disruption of cortical excitatory-inhibitory balance. Our data collectively demonstrate that endothelial cell *APOE3* serves an important purpose in the regulation of neural function in both physiological aging and neurodegeneration.

Disclosures: F.M. Marottoli: None. **H. Zhang:** None. **E. Flores-Barrera:** None. **E. Artur De La Villarmois:** None. **K. Tseng:** None. **L.M. Tai:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.01/G8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Epstein Family Research Collaboration Award

Title: Evaluation of bumetanide drug properties for repurposing as a candidate therapeutic for Alzheimer's disease

Authors: *V. HOOK[1], B. BOYARKO[2], B. GREENBERG[3], J. MOMPER[4], Y. HUANG[5], W. GERWICK[4], A. G. BANG[6], L. QUINTI[7], A. GRICIUC[8], D. KIM[7], R. E. TANZI[7], H. FELDMAN[4];
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Abstract: Therapeutics discovery and development for Alzheimer's disease (AD) has been an area of intense research to alleviate memory loss and the underlying pathogenic processes. Treatment progress has been slow with failed clinical drug development programs that have followed conventional non-clinical disease model assessments. More recent drug discovery approaches have broadened to utilize in silico computational strategies for drug candidate selection which has opened the door to repurposing and repositioning drugs for AD. Computational network analysis of gene expression signatures of patients stratified by the APOE4 risk allele of AD led to the discovery of the FDA-approved drug bumetanide as a top candidate agent that reverses APOE4 transcriptomic brain signatures and improves memory deficits in APOE4 animal models of AD. Bumetanide is a loop diuretic which acts at the kidney NKCC2 transporter for the treatment of hypertension and edema associated with cardiovascular, liver, and renal disease. Analyses of electronic health records (EHR) of large health systems revealed that patients exposed to bumetanide have lower incidences of AD by 35-70%. In the brain, bumetanide has been proposed to antagonize the NKCC1 transporter to decrease intracellular chloride ion levels which promotes GABAergic receptor mediated hyperpolarization to ameliorate disease conditions of GABAergic-mediated depolarization. NKCC1 is expressed in neurons and glia cells (oligodendrocytes, microglia, and astrocytes) in brain. In consideration of bumetanide as a repurposed drug for AD, this review evaluates its pharmaceutical properties with respect to its estimated brain levels across doses that can improve neurologic disease deficits of animal models to assess NKCC1 or non-NKCC1 mechanisms (other mechanisms). These data indicate that bumetanide efficacy may occur at brain drug levels that are below those required for inhibition of the NKCC1 transporter, which implicates non-NKCC1 mechanisms for improvement of brain dysfunctions and memory deficits. Furthermore, clinical bumetanide doses that may be efficacious to improve neurological deficits are reviewed. In summary, the efficacy of bumetanide to improve memory deficits in the APOE4 model of AD and its potential to reduce the incidence of AD in those at risk provide compelling support for clinical investigation of bumetanide as a repurposed therapeutic agent to improve AD deficits.

Disclosures: V. Hook: None. **B. Boyarko:** None. **B. Greenberg:** None. **J. Momper:** None. **Y. Huang:** None. **W. Gerwick:** None. **A.G. Bang:** None. **L. Quinti:** None. **A. Griciuc:** None. **D. Kim:** None. **R.E. Tanzi:** None. **H. Feldman:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.02/G9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Meta-analysis of NIH Alzheimer's disease-related dementias (ADRD) programs responsive to the national plan to address Alzheimer's disease (AD)

Authors: *A. MCCARTNEY, A. SHUKLA, X. YIN, S. DODSON, E. BRYANT, R. CORRIVEAU;
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Abstract: AD/ADRD diseases currently impact more than 6 million people in the United States. Rare forms of AD/ADRD are caused directly and unambiguously by genetic mutations. However, most AD/ADRD burden is complex in etiology and thought to result from an interplay among multiple incompletely understood genetic, biological, lifestyle, environmental and psychosocial risk factors. Moreover, these risk factors interact with other health factors to impact AD/ADRD outcomes. For example, while the most common dementia diagnosis is AD, research over the past decade revealed that most people with a diagnosis of AD have multiple brain pathologies, other comorbidities, and many people diagnosed with clinical AD do not have AD pathology at all. This new knowledge highlights the importance of better understanding dementia syndromes, and the relationships among them, to increase chances of developing effective interventions. The National Institute of Neurological Disorders and Stroke (NINDS) partners with the National Institute on Aging (NIA), the overall lead for NIH's response to the National Plan to address AD. NINDS leads ADRD including frontotemporal dementia (FTD), Lewy body dementias (LBD), vascular contributions to cognitive impairment and dementia (VCID) and multiple etiology dementias (MED). This project aims to evaluate NIH and the ADRD field's responsiveness to ADRD research milestones from triennial NINDS ADRD Summits by mapping NIH-funded research activities to ADRD milestones. The approach used text-based analysis/mining of grant titles, abstracts, and specific aims to map awards and activities to specific ADRD milestones. Mapping was followed by expert vetting and concurrence, including for funding opportunity announcements. The study includes new or competitively renewed NIH ADRD awards out of total $3.2 Billion toward NIH funded ADRD research from fiscal years 2017-2022. Findings will help NIH to better understand the state of the field, identify research gaps and opportunities for future efforts, and enable public communication of research activities with an accurate, accessible, compact, and updatable data visualizations. Results indicate the approach is feasible, and importantly the field and NIH have largely been responsive to the ADRD milestones in the National Plan to Address AD. The analysis points to several cross-cutting ADRD research areas that may benefit from increased attention going forward, including health equity, the multiple etiology hypothesis of common dementias, emerging risk factors for common dementias (e.g. COVID-19, traumatic brain injury, and TDP-43 proteinopathy), and clinical trials.

Disclosures: A. McCartney: None. **A. Shukla:** None. **X. Yin:** None. **S. Dodson:** None. **E. Bryant:** None. **R. Corriveau:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.03/G10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Manipulation of the diet-microbiota-brain axis in Alzheimer's disease.

Authors: D. LEE[1], V. M. LEE[2], ***S. HUR**[3];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Univ. Pennsylvania Sch. Med., Univ. Pennsylvania Sch. Med., Philadelphia, PA; [3]Neurosci. department, Genentech Inc., South San Francisco, CA

Abstract: Several studies investigating the pathogenesis of Alzheimer's disease have identified various interdependent constituents contributing to the exacerbation of the disease, including Aβ plaque formation, tau protein hyperphosphorylation, neurofibrillary tangle accumulation, glial inflammation, and the eventual loss of proper neural plasticity. Recently, using various models and human patients, another key factor has been established as an influential determinant in brain homeostasis: the gut-brain axis. The implications of a rapidly aging population and the absence of a definitive cure for Alzheimer's disease have prompted a search for non-pharmaceutical tools, of which gut-modulatory therapies targeting the gut-brain axis have shown promise. Yet multiple recent studies examining changes in human gut flora in response to various probiotics and environmental factors are limited and difficult to generalize; whether the state of the gut microbiota in Alzheimer's disease is a cause of the disease, a result of the disease, or both through numerous feedback loops in the gut-brain axis, remains unclear. However, preliminary findings of longitudinal studies conducted over the past decades have highlighted dietary interventions, especially Mediterranean diets, as preventative measures for Alzheimer's disease by reversing neuroinflammation, modifying the intestinal and blood-brain barrier (BBB), and addressing gut dysbiosis. Conversely, the consumption of Western diets intensifies the progression of Alzheimer's disease through genetic alterations, impaired barrier function, and chronic inflammation. This review aims to support the growing body of experimental and clinical data highlighting specific probiotic strains and particular dietary components in preventing Alzheimer's disease via the gut-brain axis.

Disclosures: **D. Lee:** None. **V.M. Lee:** None. **S. Hur:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.04/H1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PI: P. Aravich. CDC Nursing Home & Long-Term Care Facility Strike Team and Infrastructure Project. with with the Virginia Department of Health (VDH) and its Virginia LTC Infrastructure Pilot Project (VLIPP) program.

Title: Nursing home challenging behaviors during crises: "Compassionate Crisis Care"

Authors: ***P. F. ARAVICH**[1], B. ASHLEY[2], K. BAUSMAN[3], C. BRETZ[4], A. CLARK[5], C. COOGLE[6], J. DAVIS[7], L. HUGHES[8], C. KEETON[4], P. LEDDY[7], J. LATIMER[9], M.

MAGNER[3], A. MCDONNELL[10], M. MILLS[4], C. SHIELDS[4], A. SNYDER[9], J. STYRON[2], A. TOLLIVER[3], T. D. WEST[2], P. WESTWATER[4];
[1]Pathology and Anat., [2]Eastern Virginia Med. Sch., Norfolk, VA; [3]Virginia Med. Reserve Corps, Richmond, VA; [4]VPM Media Corp., Richmond, VA; [5]Virginia Dept. Behavioral Hlth. and Developmental Services, Richmond, VA; [6]Virginia Ctr. on Aging at VCU (retired), Richmond, VA; [7]Otto, Norfolk, VA; [8]Col. of Nursing, Hampton Univ., Hampton, VA; [9]Virginia LTC Ombudsman Office, Richmond, VA; [10]Brain Injury Assn. of Virginia (retired), Richmond, VA

Abstract: American nursing homes are in crisis (National Academies, 2022). At least 95% of residents have neurological or psychiatric disorders related to dementia (49%) (2023 Alzheimer's Disease Facts/Figures), mental illness excluding the dementias (25%) (Rahman and Anjum, 2013) or mild cognitive impairment (21%) (Chen et al., 2023). This does not count those with the behavioral complicators of stroke, traumatic brain injury and developmental disabilities. Each disorder is a risk factor for challenging behaviors under normal circumstances and especially during crises. Challenging behaviors due to psychiatric and neurological disorders are a major source of resident suffering and staff burnout. It is clear that: 1) Each disorder has a different pathophysiology that requires specialized pharmacotherapy related to, e.g., the "behavioral and psychological symptoms of the dementias" and the "neurobehavioral complications" of brain injury.2) Each disorder also responds to person-centered behavioral controls. And 3) There is excessive use of pharmacological restraints for challenging behaviors and the need for more non-pharmacological behavioral management techniques. In fact, non-pharmacological controls are more effective for dementia challenging behaviors than pharmacological controls (Watt et al., 2019). This assumes appropriate training in behavioral management techniques and sufficient staffing. However, during the COVID-19 pandemic facilities with reduced staffing and higher minority populations increased the use of pharmacological restraints (Yan et al., 2022). Hence, we developed a "Compassionate Crisis Care" behavioral management program to reduce staff burnout, reduce pharmacological restraints, and produce freely available YouTube training videos for challenging behaviors during pandemics and disasters. Our first posted video is focused on certified nursing assistants (CNAs): They are the primary professional caregivers in nursing homes. The video is designed to both train and empower them. Google: EVMS Compassionate Crisis Care. Our second video is focused on Virginia Medical Reserve Corps volunteers. Subsequent videos will focus on, e.g., the National Guard. The videos are produced in collaboration with the Richmond PBS Station, VPM Media Corporation, which is nationally recognized for its documentaries, and the internationally recognized Standardized Patient program at Eastern Virginia Medical School whereby actors model patients and providers. All videos include challenging behaviors due to Alzheimer's disease and traumatic brain injury and are under the supervision of a Statewide Steering Committee of experts.

Disclosures: P.F. Aravich: None. **B. Ashley:** None. **K. Bausman:** None. **C. Bretz:** None. **A. Clark:** None. **C. Coogle:** None. **J. Davis:** None. **L. Hughes:** None. **C. Keeton:** None. **P. Leddy:** None. **J. Latimer:** None. **M. Magner:** None. **A. McDonnell:** None. **M. Mills:** None. **C. Shields:** None. **A. Snyder:** None. **J. Styron:** None. **A. Tolliver:** None. **T.D. West:** None. **P. Westwater:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.05/H2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R34 AT010364-02S1
NIH Grant 1R34AT010364-01

Title: Patients with mild alzheimer's disease and chronic musculoskeletal pain show symptom improvement following online yoga

Authors: S. ALLENDE[1,2], L. MAHONEY[1], J. FRANCISCO[1], B. JO[2], A. K. LAU[1], ***P. J. BAYLEY**[1,2];
[1]VA Palo Alto Hlth. Care Syst., Palo Alto, CA; [2]Psychiatry and Behavioral Sci., Stanford Univ., Palo Alto, CA

Abstract: Chronic musculoskeletal pain conditions are common in patients with Alzheimer's disease (AD), and there is growing awareness that chronic pain has a major impact on cognitive function in dementia. Clinical practice guidelines are generally silent on multidisciplinary integrated care for these comorbid conditions, increasing the potential for inadequate treatment. Yoga has shown promise in treating cognitive impairment and chronic pain in AD patients, but these effects have not been demonstrated in individuals with comorbid pain and AD. We assessed the feasibility of a remotely delivered online yoga intervention for AD patients and explored the relationship between clinical outcomes. Participants were patients with mild AD (*n*=15, 57-95 years old; 77% female, mean (±SD) Mini-Mental State Exam=22.5 (±2.3)) and comorbid chronic musculoskeletal pain, and their caregivers (*n*=15, 50-75 years old; 71% Female). Patient-caregiver dyads received 12 weekly 75 min synchronous online yoga sessions, with homework on 5 non-class days. Results showed that pain severity as measured by the Brief Pain Inventory (BPI) improved from baseline (mean BPI (±SD)=4.21 (±1.9) to end-of-treatment (EOT) (mean BPI=3.29 (±1.83) ($p < .05$, Cohen's d=0.59). Mood, as measured by the Beck Depression Inventory-II (BDI) also improved from baseline (mean BDI (±SD)=18.40 (±9.96) to EOT (mean BDI =9.15 (±7.94)) ($p<.005$, Cohen's d=1.14). Changes in cognitive function were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) but did not reach statistical significance (all p's >.05). However, a trend in the direction of improved cognition following treatment was observed in tests of episodic memory (paired associate learning) (mean errors baseline=28.0 vs. EOT=18.5, $p>.05$, Cohen's d=0.45) and sustained attention (false alarms baseline = 12.5 vs. EOT=2.88, $p>.05$, Cohen's d=0.56), but not in a test of spatial working memory (mean errors baseline=18.5, EOT=21.0, $p>.05$, Cohen's d=0.2). The study met its main feasibility benchmarks of adherence to treatment (≥65% treatment sessions attended), treatment satisfaction (≥2 on treatment satisfaction indicating neutral satisfaction), recruitment rate (ability to recruit 15 dyads), retention rate (≥65% participants at EOT), and missing data rate (≤15%). In conclusion these results suggest that online yoga may be effective for treating chronic pain in patients with AD, and that such treatment can also benefit other comorbid symptoms including cognition and mood. The results also provide a rationale for a future larger randomized clinical trial.

Disclosures: **S. Allende:** None. **L. Mahoney:** None. **J. Francisco:** None. **B. Jo:** None. **A.K. Lau:** None. **P.J. Bayley:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.06/H3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Biocodex Foundation grant
Alzheimer´s Association grant (AARG-22-924247)

Title: Determination of sex hormones and their relationship with cytokine and cognitive function in women during the transition to menopause

Authors: *D. A. MORALES-MARTÍNEZ[1], A. OLEA-PÉREZ[1], I. S. ROMERO-FLORES[2], E. VERA-AGUILAR[1], A. MONSALVO-SALGADO[3], C. ESTRADA-GARCÍA[3], A. VIELMA-VALDEZ[4], R. CHAVIRA[4], J. GARCIA-MENA[2], S. G. AGUILAR-NAVARRO[3], C. PEREZ-CRUZ[1];
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Abstract: Recent studies indicate that older women are mostly affected by Alzheimer's Disease (AD); however, factors associated with sex-related vulnerability remain unknown. It has been hypothesized that changes in sex hormones production during the transition to menopause may be involved [1,2] On the other hand, estradiol (E2) and progesterone (P) regulate cytokine milieu [3,4] and AD patients show low-grade inflammation even decades before the onset of dementia [5,6]. Thus, we hypothesized that E2/P ratio regulates the proinflammatory status and cognitive function during the transition to menopause. We conducted a transversal clinical study in cognitively healthy Mexican women (30 - 65 years of age). Neuropsychological tests were followed by clinical and neurological evaluations, and MMSE was done to rule out cognitive impairment. Systemic levels of E2, Progesterone, Interleukin (IL)-1b, IL-6, and IL-10 were determined by Enzyme-linked ImmunoSorbent Assay on serum and plasm samples. Data were normalized by age, years of schooling, and the presence of the Apolipoprotein epsilon gene polymorphism (APOE). We observed that E2/P ratio was associated with proinflammatory status and alterations in specific cognitive functions according to age. These data support the proposal that alterations in sex-hormones concentrations during the transition to menopause may be involved in females' higher vulnerability to developing AD. However, we also highlight the role of E2/P ratio as an essential modulator of cytokine release that may impact cognitive function. Therefore, the optimal regulation of cytokine levels during the transition to menopause may counteract the hormonal deficit in women during the transition to menopause. References: [1] Rahman A, *et.al.*, (2020) Neurology, 95(2), e166-e178. [2] Mosconi L, *et.al.* (2021) Scientific

reports, 11(1), 1-16. [3] Yasui T, *et.al.* (2007) Maturitas, 56(4), 396-403. [4] Malutan AM, *et.al.* (2014) Menopause Review/Przegląd Menopauzalny, 13(3), 162-168. [5] Cattaneo A, *et.al.* (2017) Neurobiology of aging, 49, 60-68. [6] Walker KA, *et.al.* (2019) ACS Chemical Neuroscience, 10(8), 3340-3342.

Disclosures: D.A. Morales-Martínez: None. **A. Olea-Pérez:** None. **I.S. Romero-Flores:** None. **E. Vera-Aguilar:** None. **A. Monsalvo-Salgado:** None. **C. Estrada-García:** None. **A. Vielma-Valdez:** None. **R. Chavira:** None. **J. Garcia-Mena:** None. **S.G. Aguilar-Navarro:** None. **C. Perez-Cruz:** 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.; Biocodex Foundation grant (2020), Alzheimer´s Association grant (AARG-22-924247).

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.07/H4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Clinical and biomarker evaluation of sensory-evoked steady state gamma oscillation in Alzheimer’s Disease patients

Authors: *M. HAJOS[1,2], A. BOASSO[1], E. HEMPEL[1], C. SESHAGIRI[1], A. CIMENSER[1], M. SHPOKAYTE[1], B. VAUGHAN[1], R. KERN[1], Z. MALCHANO[1];
[1]Cognito Therapeut., Cambridge, MA; [2]Yale Univ. Sch. of Med., New Haven, CT

Abstract: Developing safe and disease modifying therapies for Alzheimer’s disease (AD) is still challenging, in spite of recent advancements in the understanding of AD pathophysiology. Modulation of functional network abnormalities may provide new strategies for disease-modifying treatments in AD. Cognito Therapeutics is developing a novel treatment option, based on recent experimental findings demonstrating that sensory-evoked 40Hz steady-state oscillation alleviates AD pathology in AD-related transgenic mice (Adaikkan & Tsai, 2020). A phase I/II clinical trial (Overture, NCT03556280) was designed to evaluate the feasibility, safety, and efficacy of Cognito Therapeutics Proprietary Gamma Sensory Stimulation System in participants with clinical presentation of AD. In the 6-month, randomized, sham-controlled trial, participants were randomized 2:1 (active:sham) to receive daily, one-hour treatment using Cognito’s Sensory Stimulation System that elicits 40Hz steady-state oscillations through audio-visual stimulation or sham stimulation. 135 participants were screened, 74 were randomized and 53 completed (20 sham arm, 33 active arm) the study. The safety of daily use of the Gamma Sensory Stimulation System was confirmed. MRI data was used to confirm the absence of ARIA and to evaluate the effects of treatment on brain structure. High adherence to daily therapy was established based on device-recorded usage. Clinical assessments included a broad range of efficacy outcome measures since no previous trials evaluated clinical benefits of this treatment. Prespecified

primary outcome measures, including MADCOMS, ADAS-Cog14 and CDR-SB showed similar decline from baseline in both sham and active arms without significant separation. Key secondary measure ADCS-ADL scores showed a reduced decline in active arm participants compared to sham arm participants. Similarly, MMSE scores showed a significantly greater decline in sham than in active arm participants. Quantitative MRI analysis revealed significantly less whole brain, and occipital lobe volume loss, along with a significantly attenuated reduction in occipital cortical thickness in the active arm compared to sham. Significant correlations between volumetric changes and outcomes in cognition and function were also demonstrated. These clinical benefits were achieved without reduction in amyloid plaque load assessed by amyloid PET scan. Our results demonstrate that daily treatment with Cognito's Proprietary Gamma Sensory Stimulation System that elicits 40Hz steady-state oscillations was safe and well-tolerated and demonstrated potential clinical benefits in AD.

Disclosures: **M. Hajos:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **A. Boasso:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **E. Hempel:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **C. Seshagiri:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **A. Cimenser:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **M. Shpokayte:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **B. Vaughan:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **R. Kern:** A. Employment/Salary (full or part-time):; Cognito Therapeutics. **Z. Malchano:** A. Employment/Salary (full or part-time):; Cognito Therapeutics.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.08/H5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: EU Horizon 2020 grant agreement No. 857375
KU Leuven C24/18/098
Belgian Fund for Scientific Research - Flanders (G0A4118N, G0A4321N, G0C1522N)
Hercules Foundation (AKUL 043)

Title: Patients in the prodromal stage of Alzheimer's disease show weaker response to gamma entrainment

Authors: *T. MLINARIC[1], L. SPRUYT[1,2], M. REINARTZ[1,2], E. KHACHATRYAN[1,3], B. WITTEVRONGEL[1], R. VANDENBERGHE[1,2,4], M. M. VAN HULLE[1];
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Abstract: Recently, a therapeutic technique based on “Gamma ENtrainment Using Sensory stimuli” (GENUS) has been proposed for Alzheimer’s disease (AD), following promising outcomes in mouse models. During GENUS, subjects are presented with periodic sensory stimulation at 40 Hz. Even though GENUS effectively reduced amyloid load in mice, studies in humans have not been conclusive. We recruited 7 prodromal, biomarker-proven AD patients (43 % female, mean age 71.29 ± 6.65, MMSE 27 ± 3.06) and 17 age-matched, cognitively normal (CN) controls (64.71 % female, mean age 70.65 ± 7.27, MMSE 29.53 ± 0.72), and subjected them to 3 different visual GENUS stimulation conditions while their EEG was recorded using a 128-channel set-up. Conditions were (1) regular 40 Hz stimulation, (2) idem with an attention task, and (3) random 30-50 Hz stimulation, with stimulation in each condition lasting 5 minutes. Stimulation was displayed using an 8 × 8 white LED matrix. For the attention condition, participants were instructed to count the number of times a red LED flashed, located in the middle of the matrix. EEG data was cut into 30 s segments with 50 % overlap, the frequency spectrum for each electrode extracted, and the results averaged. As expected, the regular 40 Hz stimulation conditions elicited a clear peak at 40 Hz while the irregular stimulation did not elicit any discernible response in its range. Next, the signal-to-noise ratio (SNR) was computed as the ratio of the spectral amplitude at 40 Hz and the average of the surrounding amplitudes (38-42 Hz), excluding 40 Hz. Comparing AD and CN groups’ SNRs, the cluster-based permutation test showed a statistically significant difference ($p < 0.01$) between AD and CN for both 40 Hz conditions, with CNs exhibiting higher SNRs. The group difference in SNR was mostly pronounced occipitally, spreading occipito-parietally in the condition with attention task. These results suggest that GENUS elicits a stronger response in CNs compared to prodromal AD patients. Furthermore, the addition of an attention task propagates the entrainment further in the brain, past the occipital region.

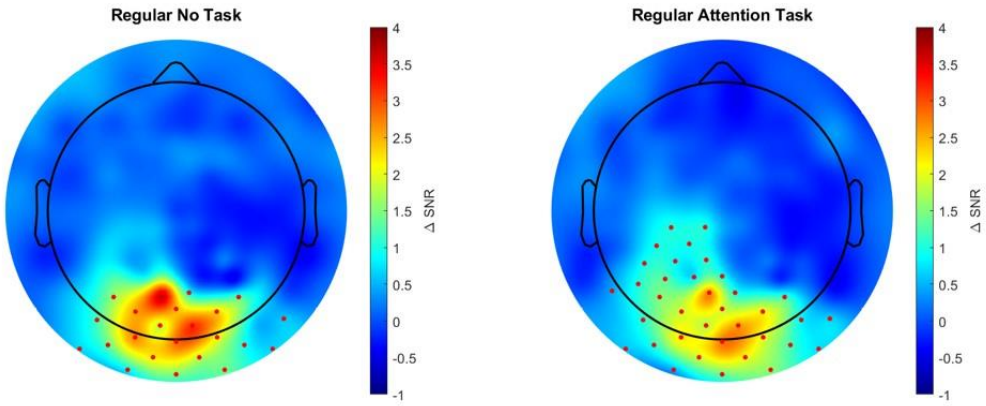


Figure 1: Spatial distribution of the group difference in SNR for two regular conditions.

Disclosures: **T. Mlinaric:** None. **L. Spruyt:** None. **M. Reinartz:** None. **E. Khachatryan:** None. **B. Wittevrongel:** None. **R. Vandenberghe:** None. **M.M. Van Hulle:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.09/H6

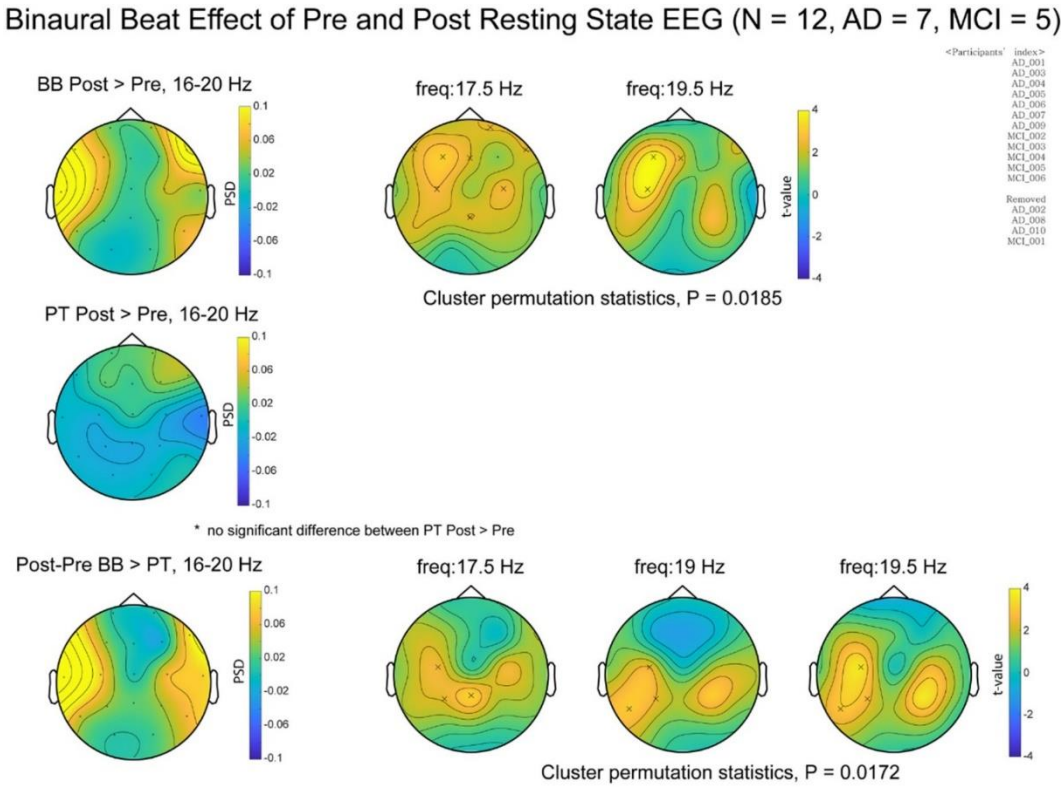
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AWARE Dallas and Neuroscience Innovation Foundation

Title: The effect of beta binaural beat stimulation on resting-state brain activity in patients with mild cognitive impairment or Alzheimer's Disease

Authors: *C. LEUNG, J.-H. KIM, J. HAPPE, J. KOVAR, Y. S. LEE;
The Univ. of Texas at Dallas, Richardson, TX

Abstract: There is a growing interest in using non-invasive brain stimulation for Alzheimer's disease (AD). Here, we used another non-invasive method, called binaural beat stimulation that is thought to entrain specific neural systems through sound. Binaural beats refer to illusory tones when two slightly mismatched frequencies are dichotically presented. Although binaural beat has been shown to improve cognition and psychological states in healthy and clinical populations, the effectiveness of binaural beat stimulation in AD and/or mild cognitive impairment (MCI) remains to be determined. In this pilot resting-state EEG (electroencephalogram) study, we measured the change of resting-state brain power between binaural beat stimulation in people diagnosed with MCI and AD. We used 18 Hz (beta) binaural beat to explore its clinical efficacy in cognitive and language intervention for these patients. Twelve patients (7 AD, 5 MCI) underwent two resting-state EEG experiments on different days (roughly a week apart), one for the binaural beat condition and another for the pure tone (control) condition. The order was counterbalanced across participants. In both conditions, participants were asked to close their eyes for a pre-resting-state EEG recording, followed by 10-minute auditory stimulation (e.g., binaural beat played with slow, non-rhythmic music), and a post-resting-state EEG recording. Results revealed a significant increase in beta power (16-20 Hz) in the bilateral frontotemporal cortex after the beta binaural beat stimulation, compared with the pure tone stimulation (see figure). Together, this finding lays the foundation for future studies in investigating the clinical efficacy of beta binaural beat stimulation in MCI and AD populations in improving their language functioning, an area that is unexplored.



Note: BB = binaural beat; PT = pure tone; PSD = power-spectrum density.

Disclosures: **C. Leung:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas. **J. Kim:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas. **J. Happe:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas. **J. Kovar:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas. **Y.S. Lee:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.10/H7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: , Doris Duke Clinical Scientist Development Award (15367)
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Ko Han Family
Lester Gimpelson

Title: Long-term effects of gamma frequency sensory stimulation after 30 months in patients with mild probable Alzheimer's disease

Authors: *D. CHAN[1,2], B. JACKSON[1], G. DE WECK[1], M. COLBURN[1], N. MILMAN[4], V. FERNANDEZ[1], E. KITCHENER[5], E. N. BROWN[6,3], E. S. BOYDEN[1,7], L.-H. TSAI[1];
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Abstract: BACKGROUND: Non-invasive gamma frequency light and sound stimulation at 40Hz was shown to reduce Alzheimer's disease (AD) pathology and improve performance during behavioral testing in mouse models of AD. Sensory stimulation inducing 40Hz entrainment reduced amyloid burden and hyperphosphorylated tau and prevented brain atrophy in different models of AD. Based on these studies, we hypothesized that induced gamma neural activity with light and sound can be used as a disease-modifying therapeutic for AD.
METHOD: We conducted a placebo-controlled, randomized control trial in subjects with probable mild AD to use our light and sound device at home for one hour daily (NCT 04042922). In the open-label extension phase, we report results after 30 months of daily 40Hz synchronized light and sound in late-onset AD (n=3) and early-onset AD (n=2) patients. Longitudinal electroencephalogram (EEG) was used to evaluate for safety and neural activity when using the 40Hz stimulation. Phone questionnaires were used to assess safety. Magnetic resonance imaging (MRI) was used to evaluate brain structure and actigraphy was used to record sleep. Cognitive evaluations included the mini mental state exam (MMSE), Montreal cognitive assessment (MoCA), Alzheimer's disease cooperative study cognitive behavior (ADAS-Cog) test and the Clinical Dementia Rating scale (CDR).
RESULT: Chronic 40Hz light and sound stimulation was safe and well-tolerated after 30 months of daily usage. EEG data show that our novel light and sound device continue to safely and effectively induced 40Hz neural activity. After 30 months of daily stimulation, 40Hz stimulation slowed brain atrophy as compared to historical age-matched controls. There was improvement of intradaily stability in 3 out of the 5 participants. Performance on cognitive testing scores improved in late-onset AD patients but not as much in early-onset AD patients.
CONCLUSION: Gamma frequency light and sound stimulation can be used safely daily for 30 months and slows AD-related degeneration. Induced neural activity using sensory stimulation at 40Hz shows promise as a novel disease modifying therapeutic for Alzheimer's dementia.

Disclosures: **D. Chan:** None. **B. Jackson:** None. **G. de Weck:** None. **M. Colburn:** None. **N. Milman:** None. **V. Fernandez:** None. **E. Kitchener:** None. **E.N. Brown:** None. **E.S. Boyden:** F. Consulting Fees (e.g., advisory boards); SAB for Cognito Therapeutics. **L. Tsai:** F. Consulting Fees (e.g., advisory boards); SAB for Cognito Therapeutics.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.11/H8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Transplanted human pluripotent stem cell-derived GABAergic neuronal precursors develop electrophysiological properties of MGE pallial-type interneurons in host mouse brains

Authors: ***C. CHEN**[1], L. FUENTEALBA[2], Y. QIU[1], K. SHEN[1], D. CHERKOWSKY[2], Y. MAURY[2], M. BERSHTEYN[2], C. R. NICHOLAS[2], J. PALOP[1];
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Abstract: During brain development, precursors of non-fast and fast-spiking GABAergic cortical interneurons are generated in the medial ganglionic eminence (MGE) and, following transplantation, retain a remarkable capacity for migration and integration in adult host brains, where they fully mature into functional inhibitory interneurons and have been shown to ameliorate multiple rodent models of neurological disorders. Thus, transplantation of human MGE-type interneuron precursors represents a novel cell therapy strategy for neurological disorders linked to impaired inhibitory function, including epilepsy, autism, schizophrenia and Alzheimer’s disease. Neurona Therapeutics has developed a clinical cell therapy candidate, NRTX-1001, comprising human pluripotent stem cell (hPSC)-derived post-mitotic GABAergic interneurons of a specific MGE pallial-type lineage. NRTX-1001 was cleared for clinical research by the FDA and is currently being evaluated in an ongoing Phase I/II trial for drug-resistant focal epilepsy. Here, we describe preclinical electrophysiological characterization of research-grade hPSC-derived interneurons in culture and in the mouse cortex for up to 18 months post-transplant. We demonstrate the progressive functional maturation of the grafted human cells and protracted acquisition of two divergent firing properties and waveforms, including fast-spiking and non-fast spiking MGE pallial-type interneurons. Our data highlight the remarkable capacity for transplanted human interneuron precursors to mature and functionally integrate into adult circuits and support further preclinical and clinical development of human GABAergic interneuron cell therapy for neurological disorders characterized by deficient inhibitory function.

Disclosures: **C. Chen:** None. **L. Fuentealba:** None. **Y. Qiu:** None. **K. Shen:** None. **D. Cherkowsky:** None. **Y. Maury:** None. **M. Bershteyn:** None. **C.R. Nicholas:** None. **J. Palop:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.12/H9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: This study is generously supported by Anne and Eugene Fife

Title: Virtual music therapy for autobiographical memory and neuropsychiatric symptoms in mild cognitive impairments and Alzheimer's disease

Authors: *K. KANG[1], S. BAKHSHI[1], D. J. LI[1], K. DEVLIN[1], B. WINSTON[2], F. S. BARRETT[2], P. B. ROSENBERG[2], A. PANTELYAT[1];
[1]Dept. of Neurol., [2]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Music therapy has shown promise for improving cognitive functioning, quality of life, and neuropsychiatric symptoms in individuals with dementia. We are investigating the potential brain network impact and effectiveness of individualized virtual MT (VMT) sessions for autobiographical memory and neuropsychiatric symptoms in individuals with mild cognitive impairment and mild dementia due to Alzheimer's disease.
Participants and caregivers attended 16 VMT sessions (two 30-minute sessions per week) with certified music therapists. Neuropsychiatric symptom assessments and MRI scans were conducted pre and post VMT sessions. For functional MRI, participants listened to 3 autobiographically salient songs, 3 digitally scrambled autobiographically salient songs, and 3 non-preferred songs. The 9 stimuli (1 minute each) were played in pseudorandomized order. After the scan, participants listened to brief excerpts from each song they heard in the scanner and rated how they felt about each excerpt. Participants (2 males, age (Mean±SD=73.50±6.36), MoCA (20±0.00)) showed decreased anxiety (STAI Scores: Pre=41.00±0.00, Post=38.50±10.61) and depressive symptoms (GDS score: Pre=4.50±2.12, Post=2.50±2.12) with increased nostalgia (Pre=25.50±6.36, Post=29.50±6.36) after VMT. Participants also reported increases in quality-of-life scores (Pre=39.50±7.78, Post=40.00±7.07) (Figure1). Initial group statistical comparisons and MRI analyses are planned after the 5th participant completes the study.
Understanding the neural network impact and neuropsychiatric symptom changes of tailored VMT may inform future interventions and improve the overall well-being of patients with these conditions.
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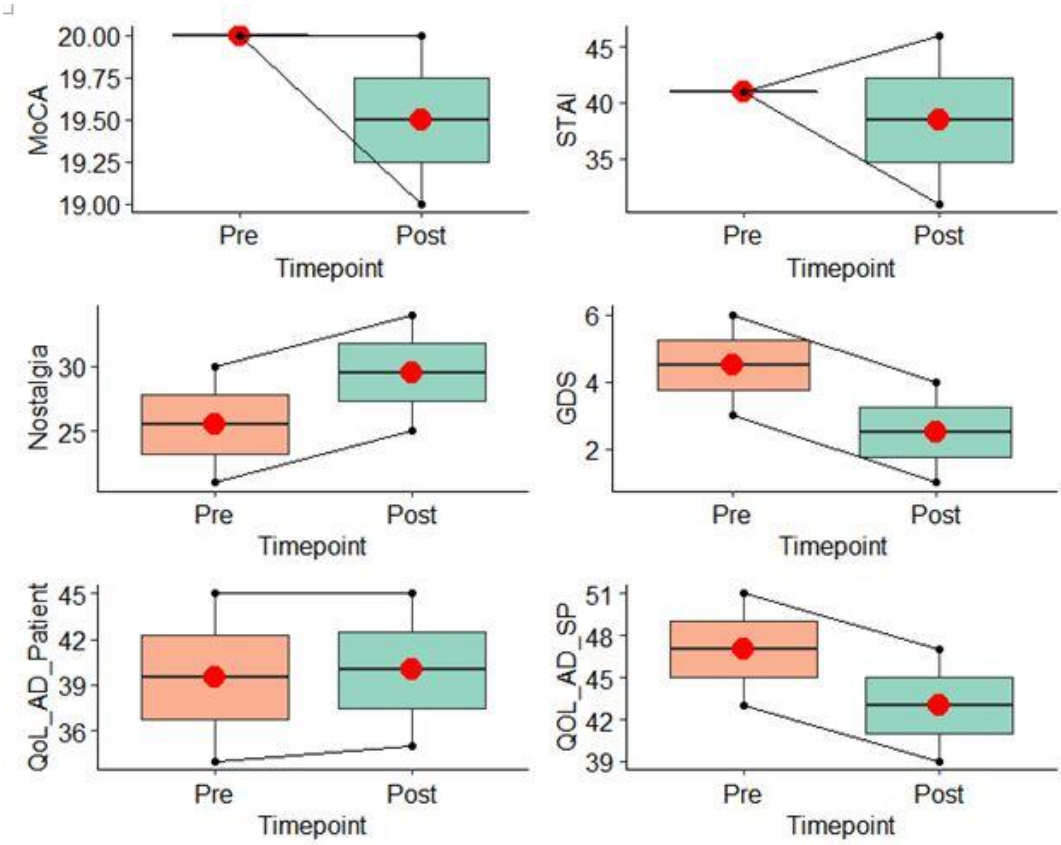

***Figure 1*. Neuropsychiatric symptom assessments before and after 16 virtual music therapy sessions.**
Note. Box plot with mean (red dot) and line graph. MoCA= Montreal Cognitive Assessment, STAI= State-Trait Anxiety Inventory, GDS = Geriatric Depression Scale, QoL_AD_Patient = Quality of Life in Alzheimer's Disease (patient version), QoL_AD_SP = Quality of Life in Alzheimer's Disease (family version).

Disclosures: K. Kang: None. **S. Bakhshi:** None. **D.J. Li:** None. **K. Devlin:** None. **B. Winston:** None. **F.S. Barrett:** None. **P.B. Rosenberg:** None. **A. Pantelyat:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.13/H10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Major SEAD Award, Institute for Creativity, Arts and Technology - Virginia Tech
UL1TR003015
KL2TR003016

Title: Musical approaches to getting in sync: Using music therapy to re-establish interpersonal behavioral and neural synchrony for persons with dementia and their caregivers.

Authors: *J. R. S. CULLIGAN[1], N. TASNIM[1], P. WINTER[4], T. UPTHEGROVE[1], L. SANDS[2], B. KNAPP[1], D. F. ENGLISH[5], J. C. BASSO[3];
[2]Ctr. for Gerontology, [3]Human Nutrition, Foods & Exercise, [1]Virginia Tech., Blacksburg, VA; [4]Carilion Clin., Roanoke, VA; [5]Neurosci., Virginia Tech. Neurosci. PhD Program, Blacksburg, VA

Abstract: The impact of dementia on the well-being of and connection between caregiver-carepartner pairs is profound. Pharmacological interventions deployed to address symptoms associated with this illness are often ineffective, with negative side effects. The failure rate of translating animal model research to develop these interventions is significant. Moreover, challenges supporting persons with dementia (PWD) to engage in this imperative research is high. For persons in long-term partnerships, the progression of this disease can negatively alter established interpersonal relationships with feelings of estrangement, distress, and confusion. Despite cognitive changes PWD experience, there is evidence that music memory is not only preserved, but it is surprisingly robust. Anecdotally, music brings PWD "back" with caregivers expressing connection when making music with their PWD. Hypothesizing caregiver-PWD pairs would show an increase in interpersonal behavioral and neural synchrony through passive and active music engagement, our team engaged three 55+, age-matched caregiver-PWD pairs in 12-weeks of music therapy sessions led by a trained music therapist (1 session per week, ~1 hour each). During sessions, we collected 8-channel electroencephalography (EEG) data (Cognionics, San Diego, CA) from the PWD, caregiver, and music therapist, aligning the signals such that the hyperscanning approach could be applied. Additionally, 360 degree video and audio was recorded so later motion-capture could be analyzed. Laban Movement Analysis was utilized to detect non-verbal communication between participants, analyzed in 20-second epochs. Behaviorally, initial findings in one caregiver-PWD pair from session 1 to 12, indicate an increase in the number of times PWD initiates nonverbal communication by attending their gaze and head movements toward not just their own partner, but to other group members. Additionally, there was an increase in gaze and head movement communication during the music portions of the session compared to the non-music (transition) portions of the session. Inter-brain synchrony was determined by calculating coherence across the same EEG channels across the caregiver, PWD, and music therapist. inter-brain synchrony occurred primarily in the theta (4-8 Hz) and alpha (8-12 Hz) frequency bands, especially in frontal brain regions. Future analyses will assess the relationships between behavioral and neural synchrony. Collectively, these findings suggest that music therapy interventions may help support interpersonal synchrony at the level of the brain and behavior and critically help caregivers reconnect with their PWD.

Disclosures: J.R.S. Culligan: None. **N. Tasnim:** None. **P. Winter:** None. **T. Upthegrove:** None. **L. Sands:** None. **B. Knapp:** None. **D.F. English:** None. **J.C. Basso:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.14/I1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Phosphodiesterase-5 inhibitor use is associated with a 68-72% relative decrease in the rate of Alzheimer's disease and related dementias: a cohort study supporting the need for a phase 3 clinical trial

Authors: *D. S. HENRY, R. G. PELLEGRINO;
Baptist Hlth. Ctr. for Clin. Res., Little Rock, AR

Abstract: Background: Preclinical studies have provided support for the use of phosphodiesterase-5 inhibitors (PDE5i) to decrease the risk of Alzheimer's disease (AD), but two recent retrospective cohort studies evaluating the association of PDE5i use with AD and Alzheimer's disease and related dementias (ADRD) reported opposing conclusions. We recently performed an unmatched case-control study using the electronic medical record database of a large healthcare system which demonstrated reduced odds of PDE5i use among patients with AD or ADRD versus patients with no ADRD in three patient populations with PDE5i indications: erectile dysfunction (ED), benign prostatic hyperplasia (BPH), and pulmonary hypertension (pHTN). Due to limitations in the data analysis platform, we were unable to establish a temporal relationship between exposure and outcome in our previous study.
Methods: We conducted a retrospective cohort study using the electronic medical record database from a large healthcare system to evaluate whether previous PDE5i use is associated with a decreased rate of AD and ADRD among patients with ED, BPH, and/or pHTN over six years of follow-up.
Results: We observed a 68-72% relative hazard reduction for AD and ADRD associated with a history of PDE5i use among populations with ED (n[$PDE5i^+$]=6068, n[$PDE5i^-$]=3698), BPH (n[$PDE5i^+$]=3540, n[$PDE5i^-$] =15479), and pHTN (n[$PDE5i^+$]=407, n[$PDE5i^-$]=3347). Survival free from ADRD was higher for patients with than for patients without a history of PDE5i use among 50-60- and 60-70-year-old patients with ED and among 50-60-, 60-70-, and 70-80-year-old patients with BPH. As pHTN is the only chronic PDE5i indication for women, we stratified by sex and observed higher survival free from ADRD among female patients with than those without a history of PDE5i use.
Conclusions: History of phosphodiesterase-5 inhibitor use (sildenafil [Viagra], tadalafil [Cialis], and vardenafil [Levitra]) was associated with a 68-72% relative hazard reduction for Alzheimer's disease and related dementias among patient populations with erectile dysfunction, benign prostatic hyperplasia, and pulmonary hypertension. Lower rates of Alzheimer's disease and related dementias were observed among both male and female patients and across a wide range of ages. These findings support the need for a phase 3 clinical trial evaluating the use of phosphodiesterase-5 inhibitors in the prevention and treatment of Alzheimer's disease and related dementias.

Disclosures: D.S. Henry: None. **R.G. Pellegrino:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.15/I2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BioVie, Inc

Title: Blinded response data from the phase 3 NM101 trial of anti-inflammatory bezisterim (NE3107) in patients with mild to moderate Alzheimer's disease

Authors: C. L. READING, *J. PALUMBO, N. OSMAN, C. AHLEM;
BioVie, Carson City, NV

Abstract: Clinical diagnosis of Alzheimer's disease (AD) and related dementias in community-based medicine is still largely based on clinical presentation and exclusion of acute vascular factors. The majority of new dementia patients lack biomarkers that qualify them for treatment with recently approved anti-amyloid antibody therapies, creating a large unmet need for safe and effective AD therapies that can be broadly used in the community-based setting. Bezisterim (NE3107) is an orally bioavailable, blood-brain barrier-permeable anti-inflammatory agent with a new mechanism of action believed to inhibit extracellular signal-regulated kinase (ERK) activation, specifically in inflammation signaling pathways, without impacting homeostatic ERK functions. We collected baseline amyloid beta (Aβ), metabolic, inflammatory, and morphometric data from a phase 3, placebo-controlled, 7-month study of bezisterim in 400 patients with mild to moderate probable AD (Study NM101 [NCT04669028]). Baseline characteristics indicated differences in disease severity, as well as metabolic and inflammatory parameters between Aβ-positive and -negative subjects, which could largely be attributed to the subjects' age; Aβ-positive subjects were older with more advanced disease. Overall, the baseline metabolic, inflammatory, and morphometric data for the 2 populations were not fundamentally different. Analysis of blinded data indicated significant improvements from baseline in the Clinical Dementia Rating (CDR) global score (−0.170, $p<0.0001$), CDR Scale Sum of Boxes (−0.861, $p<0.001$), 12-item cognitive subscale of the AD Assessment Scale (−2.75, $p<0.0001$), AD Cooperative Study (ADCS)-Clinical Global Impression of Change (−0.650, $p<0.0001$), ADCS-Activities of Daily Living (+2.750, $p<0.0001$), Mini-Mental State Examination (+2.331, $p<0.0001$), AD Composite Score (−0.126, $p<0.0001$), Mild AD Composite Score (−1.860, $p<0.0001$), Moderate AD Composite Score (−0.672, $p<0.028$), fructosamine (−3.877, $p<0.004$), and C-reactive protein (−1.347, $p<0.036$) in response to bezisterim treatment and its anti-inflammatory activity, which were similar in Aβ-positive and -negative populations. These data suggest that the pathophysiology of dementia and cognitive impairment in probable AD are driven by inflammatory factors that are present in both Aβ-positive and -negative populations. Additionally, the study findings suggest that the current diagnostic criteria for AD based on Aβ status may be too stringent and may inadvertently prevent development of therapies for patients with probable AD.

Disclosures: C.L. Reading: A. Employment/Salary (full or part-time):; BioVie, Inc. **J. Palumbo:** A. Employment/Salary (full or part-time):; BioVie, Inc. **N. Osman:** A.

Employment/Salary (full or part-time):; BioVie, Inc. **C. Ahlem:** A. Employment/Salary (full or part-time):; BioVie, Inc.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.16/I3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG077002

Title: Resveratrol differentially affects MMP release from neurons and glia; implications for therapeutic efficacy

Authors: *M. AMONTREE[1], M. NELSON[1], L. STEFANSSON[2], D. T. S. PAK[3], K. MAGUIRE-ZEISS[5,2], R. S. TURNER[4], K. CONANT[2];
[1]Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Washington, DC; [2]Neurosci., [3]Dept. of Pharmacol. and Physiol., [4]Neurol., Georgetown Univ. Med. Ctr., Washington, DC; [5]Biol. Dept., Georgetown Univ., Washington, DC

Abstract: Resveratrol, a naturally occurring polyphenol that activates sirtuin 1 (SIRT1), has been shown to reduce overall levels of matrix metalloproteases-2 and -9 (MMP-2 and MMP-9) in cerebrospinal fluid (CSF) samples from patients with Alzheimer's dementia (AD). Depending on the site of release, however, MMP-9 has the potential to improve or impair cognition. In particular, its release from microglia or pericytes proximal to the blood brain barrier can damage the basement membrane, while neuronal activity dependent release of this protease from glutamatergic neurons can instead promote dendritic spine expansion and long-term potentiation of synaptic plasticity. In the present study, we test the hypothesis that resveratrol reduces MMP levels in CSF samples from patients with APOE4, an allele associated with increased glial inflammation. We also examine the possibility that resveratrol reduces inflammation-associated MMP release from cultured glia, but spares neuronal activity dependent release from cultured cortical neurons. We observe that resveratrol decreases overall levels of active MMP-9 in CSF samples from patients with APOE4/APOE3 > APOE3/APOE3. Reservatrol also reduces CSF levels of tissue inhibitor of metalloproteinases-1 (TIMP-1), a glial derived protein, in an APOE4 allele dependent manner (APOE4/APOE4 > APOE3/APOE4 > APOE3/APOE3). Consistent with these results, we observe that resveratrol reduces basal and lipopolysaccharide (LPS)-stimulated MMP release from cultured microglia and astrocytes. In contrast, however, resveratrol does not inhibit NMDA stimulated release of MMP-9 from cortical neurons. Overall, this data is consistent with the possibility that while resveratrol reduces potentially maladaptive MMP release, adaptive MMP release is spared. In addition, this data suggests that further studies may be warranted to determine if resveratrol's effects on glial MMP-9 release could support clinical trials to determine whether if it would be a useful adjunct to AD and/or anti-amyloid therapy related damage to the blood brain barrier.

Disclosures: **M. Amontree:** None. **L. Stefansson:** None. **D.T.S. Pak:** None. **K. Maguire-Zeiss:** None. **R.S. Turner:** None. **K. Conant:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.17/I4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PHC Carlos Finlay #47069SA

Title: Amylovis-201, a potential compound for the treatment of Alzheimer's disease, is a potent sigma-1 protein agonist with anti-amyloidogenic activity

Authors: L. GARCIA PUPO[1], L. CROUZIER[2], J. MEUNIER[2], A. MORILLEAU[2], B. DELPRAT[2], A. BENCOMO MARTINEZ[1], M. SABLON CARRAZANA[1], R. MENENDEZ SOTO DEL VALLE[1], E. ORTA SALAZAR[3], S. DIAZ CINTRA[3], ***T. MAURICE**[2], C. RODRIGUEZ TANTY[1];
[1]Ctr. of Neurosci., Habana, Cuba; [2]MMDN, Univ. Montpellier, EPHE, INSERM, Montpellier Cedex 5, France; [3]Inst. of Neurobio., Univ. Nacional Autonoma di Mexico, Mexico, Mexico

Abstract: Aggregation of amyloid-ß (Aß) peptides is associated with neurodegeneration in Alzheimer's disease (AD). We identified novel naphthalene derivatives, including Amylovis-201, able to form thermodynamically stable complexes with Aß1-42 fibrils, according in silico studies. Amylovis-201 showed a high potency to: inhibit $Aß_{1-42}$ aggregation in human microglia, decrease Aß burden in 3xTg-AD mouse brain and attenuate cognitive deficits in mice [Rivera-Marrero et al., Bioorg Med Chem 2020]. The drug has a naphthalene group chemical scaffold monosubstituted by an amidoalkyl chain with a terminal thiocarbamate group. The structure of the molecule allows hydrogen bonds and hydrophobic interactions, which seems suitable for effective binding to the sigma-1 receptor (S1R) chaperone. It resembles the current agonists developed as neuroprotective drugs in AD. We investigated a putative action of Amylovis-201 at S1R. S1R agonist activity is defined by ligand ability to dissociate the ER stress chaperone BiP from S1R in S1R-overexpressing cells. The prototype agonist PRE-084 (Ki 44 nM) dissociated BiP from S1R with an IC_{50} of 426 nM and its effect was blocked by the antagonist NE-100. Amylovis-201 showed an IC_{50} of 362 nM, thus a strong S1R agonist activity. *In vivo*, the drug was tested in the dizocilpine-induced amnesia in mice and in the hyperlocomotor response of *Wfs1ab*^{KO} zebrafish, two S1R responses [Maurice et al., Brain Res 1994; Crouzier et al., Science Transl Med 2022]. Amylovis-201 attenuated dizocilpine-induced deficits, in the spontaneous alternation and passive avoidance tests, at 0.03-1 mg/kg, and blocked the increase in motor response of *Wfs1ab*^{KO} zebrafish at 3 µM. Both effects were blocked by NE-100. Finally, the drug also prevented the learning and memory deficits in mice intracerebroventricularly injected with oligomerized Aß25-35 peptide, a pharmacological model of Alzheimer's disease previously used to demonstrate the efficacy of S1R agonists and modulators [Meunier et al., Br J Pharmacol

2006; Maurice et al., Pharmacol Res 2019]. These data showed that Amylovis-201 shows a potent S1R agonist activity that is likely related to the drug ability to interfere with Aß aggregation and toxicity.

Disclosures: **L. Garcia Pupo:** None. **L. Crouzier:** None. **J. Meunier:** None. **A. Morilleau:** None. **B. delprat:** None. **A. Bencomo Martinez:** None. **M. Sablon Carrazana:** None. **R. Menendez Soto Del Valle:** None. **E. Orta Salazar:** None. **S. Diaz Cintra:** None. **T. Maurice:** None. **C. Rodriguez Tanty:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.18/I5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Analyzation of tRNA modification 5-methylcytosine (m^5C) and NOP2/Sun RNA Methyltransferase 2 (NSUN2) leads to new insights in pathological aging and Alzheimer’s Disease.

Authors: ***M. JOERG**[1], L. WALZ[1], M. LANDER[1], K. ENDRES[2], M. HELM[1], K. FRIEDLAND[3];
[1]Johannes Gutenberg Univ., Mainz, Germany; [2]Univ. Med. Ctr. Mainz, Univ. Med. Ctr. Mainz, Mainz, Germany; [3]Johannes Gutenberg-University, Mainz, Germany

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disease, characterized by gradual cognitive decline and later dementia. About 15% of the over-65s and over 50% of the over-80s are affected by AD worldwide. Despite intensive basic research, the pathogenesis of AD is only partially understood, and no high-efficacy treatment options are available. New approaches focus on the ribonuclease angiogenin (ANG) and RNA modifications in pathological aging and AD development. Especially tRNA modifications play a crucial role in RNA function and stability, but their role in pathological aging and AD remains unknown. To incorporate RNA modifications, specific proteins are required. This group of proteins is collectively known as RNA-modifying proteins (RMPs) and is further subdivided into three distinct groups: “writers”, “readers”, and “erasers”. "Writers" chemically label RNA; “erasers” remove them again; and “readers” selectively recognize and bind to certain specific chemical RNA modifications leading to producing a cellular response. Therefore, we used an Liquid Chromatography with tandem coupled mass spectrometry (LC-MS/MS) based approach in different aging and AD cell, animal, and human postmortem brain tissue models to determine whether specific tRNA modifications contribute to mitochondrial defects following the dynamic changes in modification patterns along the pathological process of aging and AD. The tRNA modification 5-methylcytosine (m^5C) located in the anticodon and variable loop region at positions 34/38/48/49/50 plays a crucial role in the stress-induced ANG-mediated tRNA cleavage. First results of LC-MS/MS and Western Blotting revealed various changes in tRNA

modifications in pathological aging and AD, especially for m^5C and the writer NOP2/Sun RNA Methyltransferase 2 (NSUN2) in an age- and sex-specific manner. Our group also determined an age-, sex- and AD-dependent dysregulation of ANG expression. These results suggest that ANG and tRNA modifications act as critical factors in the further development of AD or other neurodegenerative diseases. This line of research could be a new road to defining early biomarkers for AD and represent an important step toward developing new therapeutic strategies to improve the symptoms of AD patients.

Disclosures: **M. Joerg:** None. **L. Walz:** None. **M. Lander:** None. **K. Endres:** None. **M. Helm:** None. **K. Friedland:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.19/I6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: SUVN-I7016031: A novel M1-receptor positive allosteric modulator (M1-PAM) for the treatment of cognitive deficits associated with Alzheimer's disease

Authors: *R. MEDAPATI, V. R. GRANDHI, R. ABRAHAM, R. SUBRAMANIAN, V. R. C. PALACHARLA, R. K. BADANGE, K. BOJJA, T. NARASIMHULA, R. NIROGI;
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder due to the accumulation of β-amyloid peptide, neurofibrillary tangles and disruption of several neurotransmitters. AD is associated with cognitive impairments and behavioural disturbances. One approach to improve cognitive function in mild to moderate AD patients is by enhancing the cholinergic transmission using acetylcholinesterase inhibitors, but this approach has limited efficacy and dose limiting adverse effects. New drugs that target specific receptor subtypes of the cholinergic system may have advantages. Modulation of M1 muscarinic receptors is one option for developing new treatment for AD. M1 muscarinic receptors are G-protein coupled receptors and are highly expressed in central nervous system which plays a major role in cognition, attention and sensory processing. Developing and targeting selective M1 subtype ligands has been unsuccessful due to highly conservative orthosteric binding sites. The ligands which positively modulate the M1 allosteric sites may be a good therapeutic approach. SUVN-I7016031 is a novel, selective M1 positive allosteric modulator (M1-PAM). Reporter gene assay was used to assess its effect on the allosteric site of the M1 receptors. It was evaluated for its binding ability at the orthosteric site across all muscarinic receptors. The pharmacokinetic properties of SUVN-I7016031 were evaluated in rodent and non-rodent species. The effect on the modulation of soluble amyloid precursor protein-α (sAPP-α) was also evaluated in rat cortex. SUVN-I7016031 effects on cognitive deficits were evaluated using various animal models of cognition. The cholinergic side effects were also evaluated. SUVN-I7016031 is a selective M1-

PAM with no agonistic activity and has good selectivity over other muscarinic receptor subtypes M2 to M5. It has good oral bioavailability and brain penetration. It produced significant increase in cortical levels of sAPP-α in rats. SUVN-I7016031 reversed the time-induced as well as scopolamine-induced amnesia in object recognition task in rats. In social recognition task, rats treated with SUVN-I7016031 remembered the conspecific familiar juvenile and spent more time investigating the novel juvenile. SUVN-I7016031 reversed the scopolamine-induced cognitive deficits in contextual fear conditioning task. It also enhanced cerebral blood flow and no side effects were observed that are associated with direct mechanism of cholinergic stimulation. SUVN-I7016031 may be a future promising therapeutic intervention in alleviating cognitive deficits associated with AD.

Disclosures: R. Medapati: None. **V.R. Grandhi:** None. **R. Abraham:** None. **R. Subramanian:** None. **V.R.C. Palacharla:** None. **R.K. Badange:** None. **K. Bojja:** None. **T. Narasimhula:** None. **R. Nirogi:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.20/I7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG063826
ADDF Grant 20150701.01

Title: Allopregnanolone as a Regenerative Therapeutic for Alzheimer’s Disease:Rationale & Design of a phase 2 proof-of-concept clinical trial using hippocampal volume as a surrogate endpoint.

Authors: *G. D. HERNANDEZ[1], C. M. LOPEZ[1], A. RAIKES[2], D. MATTHEWS[4], R. D. BRINTON[3];
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Abstract: Hippocampal volume is a well-established imaging biomarker of neurodegeneration and hippocampal atrophy is predictive of cognitive decline in Alzheimer’s disease. Thus, we propose its use as a surrogate endpoint to test the efficacy of allopregnanolone as a regenerative therapeutic for mild AD. The study design to be carried out is a phase 2 multi-center, double-blind, parallel-group, randomized-controlled clinical trial. Approximately 20 sites will recruit 200 participants with mild AD, 100 participants per treatment arm. Eligible participants are male or female, age 55 to 80 years old, diagnosed with probable AD, with a MMSE score between 20-26 and APOE ε4 genotype carriers (3/4 and 4/4). Participants will be randomized to 4 mg Allo (administered intravenously over 30 minutes, once per week) or matching placebo, 1:1 allocation, for a 12-month period. After 12 months, all participants in the placebo group will be

crossed-over to receive Allo for the remainder of the study (6 month open-label phase). Brain imaging to evaluate the primary endpoint will be conducted at baseline, 6 and 12 months. A critical component of this trial is that all imaging sites participating in the trial are capable of performing both basic and advanced MRI sequences required in the protocol. The primary endpoint is mean rate of change in hippocampal volume at 12 months. Secondary Endpoints include mean rate of change in cognitive outcomes (CANTAB-PAL, ADAS-Cog11), functional outcomes (ADCS-iADL) and safety outcomes at 12 months. Exploratory endpoints include other imaging outcomes (regional brain volumes, white matter fiber tract diffusion measures as determined by DTI, average intrinsic connectivity as determined by resting state fMRI, and cerebral region cerebral blood flow); blood-based biomarkers of target engagement; other cognitive and functional outcomes (CDR-SB score, ADAS-Cog14 score, MMSE score, NPI-Q score, EuroQol 5-Dimension / 5-Level (EQ-5D-5L) health-related quality of life scale scores, QoL-AD score, Zarit Burden Interview Questionnaire score at 12 and 18 months. Additionally, change from baseline to 6, 12 and 18 months in open-label treatment participants switching from placebo to Allo at 12 months in the above endpoints. Outcomes from this study will validate previous findings indicating that allopregnanolone may exert both regenerative and neuroprotective effects on structure and connectivity in the Alzheimer's brain.

Disclosures: G.D. Hernandez: 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.; IH/NIA research support: R01AG075122, R01AG063826. F. Consulting Fees (e.g., advisory boards); Consultant at NeuTherapeutics, LLC. **C.M. Lopez:** F. Consulting Fees (e.g., advisory boards); Consultant at NeuTherapeutics, LLC. **A. Raikes:** None. **D. Matthews:** Other; CEO of ADMdx. **R.D. Brinton:** 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/NIA grants: P01AG026572, R37AG053589, R01AG057931, R01AG063826, R01AG075122, T32AG061897. Other; President of NeuTherapeutics, LLC.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.21/I8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A novel small molecule inhibitor mitigates toxic amyloid oligomers and behavioral abnormalities in an Alzheimer's disease mouse model

Authors: *E. SHAO[1], M. KOKES[1], S. ARYA[1], J. SCHWARZ[1], K. BURK[1], X. LIU[2], S. GAIKWAD[3], R. KAYED[3], M. T. BOWERS[2], A. SINGH[1], V. MATHUR[1], K. PLANEY[1]; [1]Acelot.Inc, South San Francisco, CA; [2]Dept. of Chem. and Biochem., Univ. of California, Santa

Barbara, CA; [3]Departments of Neurol. & Neurosci. & Cell Biol. & Anat., Univ. of Texas Med. Br., Galveston, TX

Abstract: Background: Alzheimer's disease (AD) is characterized by the accumulation of insoluble aggregates of the amyloid beta 1-42 (Aβ42) fragment of amyloid precursor protein (APP) and hyperphosphorylated tau protein, leading to synaptic and neuronal loss and inflammation in the central nervous system. The contribution of specific tau and amyloid beta species to cognitive decline in AD is still debated. However, evidence suggests that small oligomers, rather than higher-order aggregates, are primarily responsible for the toxic effect leading to neuronal death. While individual targeting of Aβ42 and tau is currently under investigation, the potential benefits of combination therapy have been underexplored. **Objectives**: the objectives of this study are to assess the in vitro potency and mechanism of action of Acelot's novel small molecule, ACE258, to determine its pharmacokinetic properties and target engagement in vivo, and to evaluate its efficacy in the 3xTg mouse model of AD. **Methods:** by employing our joint pharmacophore space (JPS) machine learning platform, we have identified novel small molecules that bind to both Aβ42 and tau oligomers. We demonstrate in vitro mechanism of action using the Thioflavin T assay, ion mobility-mass spectrometry (IM-MS), and oligomer toxicity assay. Furthermore, we evaluate the drug efficacy in vivo using a 3xTg mouse model of AD, which exhibits both Aβ and tau pathologies. **Results:** our findings indicate that ACE258 effectively reduces the fibrilization of Aβ42 in the Thioflavin T assay. IM-MS reveals that the Aβ42 peptide forms dimers to dodecamers in vitro. Coincubation with ACE258 or incubation post-oligomerization reduces toxic dodecamer oligomer species and increases Aβ42 monomers in solution. Moreover, ACE258 rescues tau oligomer-dependent toxicity in rat primary neuronal cells, highlighting its cell permeability and potent activity in neuronal models. Additionally, ACE258 mitigates tau oligomer-dependent electrophysiological abnormalities in mouse hippocampal brain slices. Oral administration of ACE258 in mice demonstrates good tolerability and brain penetration for up to 24 hours. Lastly, ACE258 ameliorates certain behavioral abnormalities in the 3xTg mouse model of AD. **Conclusion:** ACE258 is a clinical candidate drug with favorable pharmacokinetic properties and brain permeability. It functions as a poly-disaggregator that targets toxic forms of both Aβ42 and tau, inhibits fibrilization and toxic amyloid oligomers in vitro, reduces oligomer-dependent neuronal toxicity, partially restores oligomer-associated nerve conduction, and rescues behavioral abnormalities in 3xTg AD mice.

Disclosures: E. Shao: A. Employment/Salary (full or part-time):; Acelot/148k(Full time), Acelot.inc. **M. Kokes:** None. **S. Arya:** None. **J. Schwarz:** None. **K. Burk:** None. **X. Liu:** None. **S. Gaikwad:** None. **R. Kayed:** None. **M.T. Bowers:** None. **A. Singh:** None. **V. Mathur:** None. **K. Planey:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.22/J1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH1R61NS126618-01A1 R61/R33

Title: Novel LXR-PPAR agonist improves behavior deficits and synaptic plasticity in a model of Alzheimer's disease.

Authors: *R. H. AMIN[1], I. STEINKE[2], F. S. WIBOWO[3], S. YOO[3], V. SUPPIRAMANIAM[4], M. SINGH[3], R. ARNOLD[3];
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Abstract: The increased incidence of Alzheimer's disease (AD) and its associated mortality rate represent an unmet medical need and a critical need for novel molecular therapeutics. Recent work focusing on patients with the apoE4 alleles has highlighted the association of brain cholesterol dysregulation with elevated pathological burden, and neurodegeneration. These studies have highlighted the importance of the nuclear receptor Liver X receptor (LXR) for developing AD therapies. However, LXR agonists have been observed to induce hepatotoxicity and neutropenia in humans and thus have failed in clinical trials for atherosclerosis. Our newest dual agonist, AU403, was developed computationally as a novel Liver X Receptor-β (LXRβ) with partial PPARδ/α activity. Our library of compounds (>100) was created in silico and is based upon selective amino acid interactions in the ligand-binding domains of both LXRβ and PPARδ/α with negligible PPARγ activity. Thus, our design serves as a dual LXRβ/ PPARδ/α agonist. This strategy seeks to avoid the unwanted side effects of traditional LXRα and PPARγ agonists, including liver toxicity, neutropenia, edema, and heart failure. **Methods:** Our lead compound, AU403 was designed computationally using Schrodinger software and molecular dynamics to model enzymatic activity against known PPAR agonists, using crystal structures of PPAR (γ, α, δ). Further AU403, drug design was optimized by modeling ADME properties using both QikProp and GastroPlus to enhance distribution to the CNS. Improved working declarative memory was observed in 12-month 3xTgAD mice, using Y-maze and Novel object recognition studies after 3 months of AU403 treatment (5mg/kg / daily). Improvement on synaptic plasticity was measured by long-term potentiation studies. **Results:** Our *in silico* design was formulated on Based on these evaluations our lead compound AU403 displays avoidance of Trp443 and Leu439, which are deep in the LXRα-AF2 ligand binding pocket. Furthermore, we observed significant improvement in working declarative memory and long-term potentiation in 12-month old 3xTgAD mice treated with our lead compound AU403. Mechanistically we observed enhanced microglia interaction with dendritic spine density. **Conclusion**: We have observed that AU403 can serve as a highly novel potential therapeutic agent for AD.

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Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.23/J2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MGH Center for Skeletal Research Core Small Grant and NIH/NIDDK and NIH/NIA research grants (R01 DK121776) to M. Bastepe
RF1 AG056032 to A. Dedeoglu

Title: Amyloid neuropathology-induced bone loss in the 5xFAD model of Alzheimer's disease

Authors: *Y. JUNG[1,3], B. AY[4], S. M. CYR[4], C. M. TOGNONI[1,3], K. KLOVDAHL[4], J. MATTHIAS[4], Q. CUI[4], D. J. BROOKS[4], M. BOUXSEIN[4,5], I. CARRERAS[1,2,3], A. DEDEOGLU[1,3,6], M. BASTEPE[4];
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Abstract: Alzheimer’s disease (AD) and osteoporosis often coexist in the elderly population. Observational studies suggest the association between these two diseases in which i) lower bone mineral density (BMD) is associated with a higher risk of developing AD, and ii) AD patients have reduced BMD and increased incidence of falls and hip fractures compared to healthy people. However, the pathophysiologic link between AD and skeletal health has been poorly defined and the mechanisms underlying AD-associated reduction of BMD are unknown. We examined the skeletal phenotype of 5xFAD mice, an AD model with accelerated neuron-specific amyloid-beta accumulation causing full-blown AD phenotype by the age of 8 months. Micro-computed tomography indicated significantly lower trabecular and cortical bone parameters in 8-month-old male, but not female, 5xFAD mice than sex-matched wild-type littermates. Dynamic histomorphometry revealed reduced bone formation and increased bone resorption in 5xFAD males, in which quantitative reverse transcription-polymerase chain reaction (qRT-PCR) showed elevated the skeletal resorption stimulation factor, receptor activator of nuclear factor kappa-B ligand (RANKL) gene expression and a tendency for reduced expression of several osteoblast/osteocyte-specific genes, including bone sialoprotein (*Ibsp*), dentin matrix protein-1 (*Dmp1*), sclerostin (*Sost*), and the wingless-related integration site (Wnt)/beta-catenin targets AXIS inhibition protein 2 (*Axin2*) and transcription factor-7 (*Tcf7*). 5xFAD males also had reduced body fat percentage with unaltered lean mass, as determined by dual-energy X-ray absorptiometry (DXA) and showed elevated the circadian rhythm-regulating gene, uncoupling protein 1 (*Ucp1*) mRNA levels in brown fat, indicating high sympathetic nervous system activity. Moreover, male 5xFAD bones showed abnormal expression levels of multiple circadian rhythm-regulating genes, including brain and muscle arnt-like protein-1 (*Bmal1*) and RAR-related orphan receptor A (*Rora*). Together, our findings indicate that AD promotes osteopenia by affecting both bone formation and bone resorption via mechanisms likely involving increased sympathetic tone and a disrupted circadian rhythm. Our study provides novel insights into the link between AD pathophysiology and osteoporosis, which may help develop strategies to treat osteoporosis in AD patients.

Disclosures: **Y. Jung:** None. **B. Ay:** None. **S.M. Cyr:** None. **C.M. Tognoni:** None. **K. Klovdahl:** None. **J. Matthias:** None. **Q. Cui:** None. **D.J. Brooks:** None. **M. Bouxsein:** None. **I. Carreras:** None. **A. Dedeoglu:** None. **M. Bastepe:** None.

Poster

PSTR259. Therapeutic Strategies in Alzheimer's Disease and Other Dementias

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.24/J3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH
NIH (R01HL155532)
NIH (R35HL150807)

Title: Molecular dynamics and experimental validation identify the CPE/NF-a1 binding site on HTR1E responsible for b-arrestin activation and subsequent neuroprotection

Authors: X. YANG[1], J.-Y. LEE[2], S.-K. KIM[3], S. VINAY[1], *Y. LOH[1,2,3], W. A. GODDARD, III[3];
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Abstract: Carboxypeptidase E (CPE), also known as neurotrophic factor (NF-α1), is both a prohormone processing enzyme involved in the biosynthesis of neuropeptides and peptide hormones and a neurotrophic factor that has neuroprotective activity. To uncover the underlying mechanism of CPE in neuroprotection, we had previously identified an interaction between the serotonin receptor, HTR1E, and the central part of CPE, which protect human neurons against oxidative/neuroexcitotoxic stress via β-arrestin/extracellular signal-regulated kinase (ERK) signaling. We had also predicted various amino acids in CPE that are involved in the interaction with HTR1E, forming three salt bridges between the two molecules. In this study, by mutating a series of sites in the central part of CPE that are predicted to be important for CPE/HTR1E interaction, we found a single mutation of CPE K302A (M1), along with other two combination of mutations, CPE K302A+D306A+D275A (M11), CPE D259A+E260A+W319A (M15), decreased binding to HTR1E. The CPE site K302 is the most important one among 16 CPE mutants we tested, which is consistent with molecular dynamic simulation analysis. *In silico* analysis also revealed these 3 mutants might dramatically reduce activation of β-arrestin due to decreases in binding, consistent with decreased pERK1/2 level found in cells treated with these mutants. Unlike the other CPE mutants, we also found that CPE K302A is the only one that attenuates CPE's ability to protect cells from H_2O_2-induced cytotoxicity. In summary, the results confirm experimentally, validating the previously predicted CPE binding site to 5-HTR1E that is responsible for β-arrestin activation and subsequent neuroprotection. This provides the target for

experiments and *in silico* computational screening to identify small molecules to replace the CPE/ NF-α1 protein as novel drugs to protect human neurons against oxidative/neuroexcitotoxic stress via β-arrestin/ERK signaling.

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Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.01/J4

Topic: C.03. Parkinson's Disease

Support: 1R01NS122226-01

Title: Effects of interventional genetic knockdown of the serotonin transporter on L-DOPA-induced behaviors in a rat model of Parkinson's disease

Authors: *G. MCMANUS[1], A. CENTNER[1], N. LIPARI[1], C. BUDROW[1], S. VENKATESH[1], C. BISHOP[1], F. P. MANFREDSSON[2];
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Abstract: Parkinson's disease (PD) is a neurodegenerative disease typified by the loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc) that results in motor symptoms including resting tremor, rigidity, akinesia, and postural instability. Dopamine replacement therapy with L-3,4-dihydroxyphenylalanine (L-DOPA) has remained the gold-standard treatment for the motor symptoms of PD, however, chronic use leads to the development of treatment-induced side effects known as L-DOPA-induced dyskinesia (LID). The mechanisms underlying LID are multifaceted, but accumulating research has strongly implicated aberrant neuroplasticity in raphe-striatal serotonin (5-HT) circuits. This compensatory neuroplasticity may be beneficial in earlier stages of PD but becomes maladaptive and precipitates LID with continued dopamine (DA) denervation in later stages. Given that the 5-HT transporter (SERT) has an affinity for DA uptake and is upregulated in the brain of dyskinetic patients and in animal models of LID, it has emerged as an intriguing target for anti-dyskinetic adjuncts. Therefore, we employed a genetic knockdown of SERT (SERT-KD) to investigate its role in LID expression. 6-hydroxydopamine-lesioned Sprague-Dawley rats were administered sub-chronic L-DOPA daily for 2 weeks to establish LID. Following the last day of L-DOPA treatment, animals underwent a second surgery where they received either a recombinant adeno-associated virus 9 (AAV9) short-hairpin RNA driven SERT-KD (SERT-shRNA) or control scrambled shRNA AAV9-GFP (SCR-shRNA). Animals were allowed 4 weeks for optimal transfection after which they received another 2 weeks of daily sub-chronic L-DOPA treatment to track changes in LID expression. We hypothesized that this genetic intervention would reduce

LID expression by attenuating the dysregulated DA efflux from 5-HT cells, a primary presynaptic mechanism thought to underlie LID. Behavioral data showed a marked reduction in LID across the second treatment period in animals who received the SERT-KD viral condition compared to SCR-shRNA controls. This suggests a reorganization of pro-dyskinetic circuitry following SERT-KD knockdown that further supports SERT as an important mechanism in the development and expression of LID and provides a promising avenue for developing novel therapies to optimize PD treatment.

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Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.02/J5

Topic: C.03. Parkinson's Disease

Support: Internal TL1 Predoctoral Award, School of Medicine, University of Maryland, Baltimore
R36 Dissertation Grant R36AG080272

Title: Effect of Practice Schedule on Motor Learning of Reactive Balance Responses in Persons with Parkinson's Disease and Age-matched Control

Authors: *R. Y. AKINLOSOTU[1], K. P. WESTLAKE[2];
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Abstract: Objective: Persons with Parkinson's disease (PwPD) have set-shifting impairments that may limit motor learning of protective responses to prevent falls. Practice schedules (blocked and random practice), a widely used motor learning principle in sports, may enhance or limit the acquisition and retention of protective stepping responses to balance challenges. This study compares the acquisition & retention of protective stepping stability via blocked versus random practice schedules in PwPD & age-matched controls. **Methods:** Twenty PwPD & 20 age-matched controls (HC) will experience a slip & trip-like perturbations to induce stepping responses via random & blocked practice schedules. Blocked practice is repeating a task (e.g., slip) several times before the next, while random practice is randomly practicing two tasks (slip & trips). Each subject will wear a safety harness with an integrated load cell to prevent falls. Our primary outcome, the margin of stability (MoS) at 1st the protective step before, 10 minutes, & 2 days after practice, will be analyzed using two ANOVA (Group vs. Trial). **Results:** To date, we have assessed 2 & 4 healthy controls in the random (HC_RAND) & blocked (HC_BLOC) practice group, respectively & 2 PwPD each in the blocked (PD_BLOC) & random (PD_RAND) practice group. With baseline MoS normalized to 0, the mean of the normalized change score

was reported. The HC_BLOC improved their MoS from the pretest to posttest slip (0.086) at the acquisition phase, & from the pretest to retention slip test (0.067). Although HC_RAND MoS decreased from the pretest to posttest slip (by -0.011), they improved their MoS from the pretest to posttest slip (-0.02). Among PwPD, while the MoS for PD_BLOC improved from pretest to posttest (0.164) & from pretest to retention test (0.118), PD_RAND's MoS declined from pretest to posttest (-0.0275), & from pretest to retention (-0.0213). The MoS change score was higher for persons with lower MoS at baseline than those with higher MoS at baseline. **Significance of Impact:** The findings will provide knowledge that may foster the development of robust balance rehabilitation protocols to improve postural responses in PwPD & reduce fall-related delayed & ineffective stepping responses in PD.

Disclosures: R.Y. Akinlosotu: None. **K.P. Westlake:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.03/J7

Topic: C.03. Parkinson's Disease

Support: Grant ASAP-020505

Title: Functional changes of nigral dopamine neurons in a neuromelanin-producing rat model of Parkinson's disease

Authors: *A. LEDONNE[1,2,3], S. L. D'ADDARIO[2,3], M. MASSARO CENERE[2,3], F. COSSA[1,2,3], M. VILA[3,4,5], N. B. MERCURI[1,2,3];
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Abstract: Neuromelanin (NM) is a dark brown intracellular pigment that accumulates in human substantia nigra pars compacta (SNpc) dopamine (DA) neurons with age, conferring the nigral dark look that inspired area's nomenclature. NM buildup has long been associated with Parkinson's disease (PD), in light of the evidence that NM-containing neurons particularly degenerate during PD progression and Lewy bodies (LBs) mainly form in close proximity with NM. To date, the functional impact of the progressive NM accumulation on nigral DA neurons activity is completely unknown, with limitations in preclinical investigations mainly due to lack of overt NM production in rodents, oppositely to humans. In this study, we induced in vivo intranigral NM production in rats, by injections of an adeno-associated viral vector (AAV) carrying human tyrosinase (hTyr), the enzyme responsible for the peripheral melanin formation. We found that AAV-hTyr-injected rats, few weeks after AAVs injection, exhibit hTyr expression

associated with NM production in SNpc DA neurons, as proved by hTyr immunolabeling and NM detection by the Masson-Fontana staining procedure. To determine the functional consequences of NM expression on SNpc DA neurons activity, we performed ex vivo patch-clamp recordings of nigral DA neurons in midbrain slices of AAV-hTyr-injected rats and controls rats, injected with an AAV-empty vector. We found that NM accumulation produces overt functional changes of nigral DA neurons, by modifying passive membrane properties and the spontaneous firing activity, by switching the firing pattern toward increased activity/bursting mode. In parallel, we observed modifications in some intrinsic currents that physiologically control spontaneous pacemaker firing activity of nigral DA neurons. In conclusion, here we display the first evidence on a functional impact of NM accumulation on nigral DA neurons activity. As firing rate and modality critically affect DA release in the striatal projection areas, the observed functional alterations might correlate with changes in DA levels in the projection areas. Future investigations might disclose if the observed functional modifications are compensatory adaptations of nigral DA neurons, attempting to counteract initial neurodegeneration, or represent early pathological features preceding nigral DA neurons loss.

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Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.04/J8

Topic: C.03. Parkinson’s Disease

Support: CIHR IRSC
Parkinson Canada

Title: Glutamate co-transmission by serotonin neurons of the dorsal raphe nucleus contributes to L-Dopa dyskinesia expression

Authors: *L. SAIDI, V. RIOUX, M.-J. WALLMAN, S. POZZI, M. LÉVESQUE, C. PROULX, M. PARENT;
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Abstract: OBJECTIVE: Parkinson’s disease is characterized by the progressive loss of midbrain dopamine neurons that innervate the striatum. The dopamine precursor L-3,4-dihydroxyphenylalanine (L-Dopa) is the most effective pharmacotherapy but its chronic use is hampered by side effects such as abnormal involuntary movements (AIMs), also termed L-Dopa-induced dyskinesia (LID). Previous studies have shown the crucial role of serotonin (5-HT) neurons in the conversion of exogenous L-Dopa into dopamine, and in LID expression. Here, we specifically addressed the functional role of glutamate co-transmission by 5-HT neurons of the dorsal raphe nucleus (DRN) in the regulation of motor behavior and in LID expression.

METHODS: In 6-hydroxydopamine-intoxicated mice, a chemogenetic approach was first used to alter the neuronal activity of DRN 5-HT neurons while administering L-Dopa in order to specifically address the role of these neurons on LID expression. Using the same mouse model of Parkinson's disease, we then used CRIPSR-Cas9 technology and virus injections to knock-out or overexpress the atypical vesicular glutamate transporter 3 (VGluT3) in 5-HT neurons of the DRN. These mice were then treated with L-Dopa to induce AIMs. **RESULTS**: Compared to control conditions, more severe AIMs were observed when 5-HT neurons of the DRN were acutely activated by hM3Dq-DREADD. Our CRIPSR-Cas9 manipulations led to exacerbated AIMs in dopamine-lesioned VGluT3-conditional knock-out mice that were treated with a non-dyskinetic dose of L-Dopa (1mg/kg), compared to controls and to transgenic mice overexpressing VGluT3. At higher doses of L-Dopa (3, 6, 12 mg/kg), mice overexpressing VGluT3 showed more severe orofacial AIMs. **CONCLUSIONS**: Glutamate that is co-released by 5-HT neurons of the DRN is involved in the expression of LID.

Disclosures: L. Saidi: None. **V. Rioux:** None. **M. Wallman:** None. **S. Pozzi:** None. **M. Lévesque:** None. **C. Proulx:** None. **M. Parent:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.05/J9

Topic: C.03. Parkinson's Disease

Support: R01-NS122226-01A1

Title: Effects of interventional genetic expression of dopamine D2 receptors on dorsal raphe neurons on L-DOPA-induced dyskinesia in a hemiparkinsonian rat model

Authors: *A. CENTNER[1], N. LIPARI[1], F. MANFREDSSON[3], C. R. BISHOP[2]; [2]Binghamton Univ., [1]Binghamton Univ., Binghamton, NY; [3]Barrow Neurolog. Inst., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Levodopa (L-DOPA) continues to be the standard treatment for Parkinson's Disease despite the eventual development of abnormal involuntary movements (AIMs) known as L-DOPA-induced dyskinesia (LID). Serotonergic cells originating in the dorsal raphe nucleus (DRN) have been implicated in the *development* and *maintenance* of LID in both preclinical and clinical literature. Serotonin (5-HT) neurons terminating in the striatum are believed to take up L-DOPA, convert it to dopamine (DA), and release it like its native neurotransmitter 5-HT. Although this gain-of-function may be beneficial in early stages of PD, the unregulated release of DA via 5-HT terminals ultimately results in debilitating motor fluctuations that are poorly managed with current treatments. Serotonin transporter (SERT) blockers and 5-HT_{1A} agonists can reduce dyskinetic behaviors, however several compounds are shown to disrupt L-DOPA's motor efficacy, implicating a paucity of knowledge on the mechanisms through which 5-HT

compensation acts to convey L-DOPA's effects. Previous work from our group has shown that *prophylactic* expression of DA D2 autoreceptors (D2AR) can prevent the development of LID in hemiparkinsonian rats. The present work sought to *interventionally* reduce established LID, a more powerful and clinically relevant approach. To do so, tryptophan-hydroxylase-2 (TPH2)-Cre+ male and female Long Evans rats received a unilateral 6-hydroxydopamine (6-OHDA) medial forebrain bundle lesion to induce hemiparkinsonism. Following recovery, animals were split into equally lesioned groups and received daily L-DOPA (6 mg/kg; subcutaneous) or vehicle injections for 14 days to establish stable LID. AIMs were assessed on days 1, 7 and 14. After this 14-day treatment period, animals underwent a second survival surgery to infuse either Cre-dependent AAV-FLEX-D2AR or AAV-FLEX-GFP (control) into the DRN. To provide optimal transfection, animals were allowed 4 weeks of recovery, after which they were treated with their respective chronic treatments for 14 days and AIMs observed on days 1, 7, and 14 to assess their dyskinesia levels post-intervention. We assessed animals' motor performance with the forepaw adjusting steps (FAS) test pre- and post-intervention to assure L-DOPA's efficacy was not hindered. Overall, this project will determine whether autoregulation of DA release via 5-HT cells is sufficient to reduce or reverse L-DOPA-induced complications without affecting L-DOPA's benefits while further implicating 5-HT neuroplasticity in L-DOPA's effects in the parkinsonian brain.

Disclosures: A. Centner: None. **N. Lipari:** None. **F. Manfredsson:** None. **C.R. Bishop:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.06/J10

Topic: C.03. Parkinson's Disease

Title: Prediction of engraftment success guides selection of iPSC-derived dopaminergic neurons in preclinical models

Authors: *G. BEAUVAIS, J. MOSSMAN, J. STEIN, C. CHANDRASEKARAN, H. TRAN, L. ZEBROWSKI, A. BRATT-LEAL, R. WILLIAMS, X. ZHANG;
Aspen Neurosci., San Diego, CA

Abstract: Prediction of engraftment success guides selection of iPSC-derived dopaminergic neurons inpreclinical models Authors: Genevieve Beauvais*, PhD, Jim Mossman*, PhD, Jason Stein, Chandnee Chandrasekaran, PhD,Ha Tran, Louisa Zebrowski, Andres Bratt-Leal, PhD, Roy Williams, PhD, Xiaokui Zhang, PhD* First co-authors. The motor symptoms of Parkinson's disease (PD) are aresult of dopamine deficiency in the brain due to progressive degeneration ofdopaminergic neurons in the substantia nigra pars compacta and theirprojections in the putamen. Restoringthe levels of dopamine by transplanting functional dopaminergic progenitorneurons (DANPCs) into the central nervous system would potentially provide anefficient therapeutic approach to treat these symptoms. The technology nowexists for ex vivo

generation of patient-specific dopaminergic neurons byde-differentiating patient-derived somatic cells into induced pluripotent stemcells (iPSCs) followed by differentiating the iPSCs to dopaminergicneurons. Towards development of anautologous neuron replacement therapy, Aspen Neuroscience has established abattery of robust quality control assays to examine the purity, identity andefficacy of manufactured DANPCs. Among these, large reference data sets havebeen generated for developing predictive genomic analyses to evaluate genomicintegrity of DANPCs, as well as their potential ability to successfully engraftafter intracranial transplantation and be efficacious in vivo. Using a data setof nearly 800 human DANPC-derived transplants within the striatal regions ofimmunocompromised Rowett athymic nude rats, encompassing approximately 100independent differentiations of iPSCs from 12 patients with unique geneticbackgrounds across both sexes, we tested the ability of the transcriptome dataof DANPCs to predict engraftment outcomes such as graft survival and size. We found that bulk RNASeq analysis correlatedwith graft characteristics such as: (a) human nuclei counts, and (b) area withpositive human cytoplasm staining. These findings could allow successfulranking of various DANPC lots generated from the same donor for drug productconsistency, expected ability to engraft and in vivo efficacy, and couldultimately inform the selection of particular drug product lots for clinicalapplication.

Disclosures: **G. Beauvais:** None. **J. Mossman:** None. **J. Stein:** None. **C. Chandrasekaran:** None. **H. Tran:** None. **L. Zebrowski:** None. **A. Bratt-Leal:** None. **R. Williams:** None. **X. Zhang:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.07/K1

Topic: C.03. Parkinson’s Disease

Title: Subthalamic and pallidal local field potential activity associated with cognitive performance in patients with Parkinson's disease

Authors: *J. L. CHAN, K. A. JOHNSON, L. E. KENNEY, D. BOWERS, J. D. HILLIARD, K. D. FOOTE, C. DE HEMPTINNE;
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Abstract: Although Parkinson’s disease (PD) is a neurodegenerative disorder most readily characterized by motor symptoms, concurrent cognitive impairment is common, debilitating, and difficult to treat. Loss of dopaminergic neurons in the substantia nigra and associated dysfunction of cortico-basal ganglia-thalamocortical circuits are thought to underlie motor and cognitive symptoms. Lesion, functional imaging, and neurophysiological studies, along with cognitive impairment in PD, have implicated the subthalamic nucleus (STN) and globus pallidus interna (GPi) in normal cognitive control. However, the mechanisms by which the STN and GPi contribute to cognitive function and dysfunction remain poorly understood. In this study, the

relationship between STN and GPi local field potential (LFP) activity and cognitive performance was investigated by using intraoperative LFP recordings in PD patients undergoing DBS implantation surgery and their presurgical neuropsychological assessments, including measures in the domains of attention, executive function, delayed verbal memory, language, and visuospatial function. Sixty seconds of LFPs at rest in the off-medication state were recorded in monopolar configuration from 15 PD patients (3 females, mean age 64.5 years) with STN DBS and 38 PD patients (10 females, mean age 68.3 years) with GPi DBS. The power spectral density (PSD) was computed for each DBS lead contact using the Welch periodogram method with a 1 s Hanning window and 0.5 s overlap, and mean normalized power in the delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and low gamma (30-70 Hz) frequency bands was calculated across all contacts for each patient. A significant correlation was found between both STN and GPi theta power and attentional tests. Specifically, higher resting theta power was associated with worse performance on the digit span test and Trails Making Test Part A. LFP power was not associated with performance in tests of delayed verbal memory, language, or visuospatial function. These results suggest that the STN and GPi may play a role in attentional impairment in PD and that theta activity may be an electrophysiological biomarker of cognitive impairment. Cognitive impairment in PD preferentially affects attention and identifying abnormal oscillatory activity in cortico-basal ganglia-thalamocortical circuits may guide the development of neuromodulatory therapies.

Disclosures: **J.L. Chan:** None. **K.A. Johnson:** None. **L.E. Kenney:** None. **D. Bowers:** None. **J.D. Hilliard:** None. **K.D. Foote:** None. **C. de Hemptinne:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.08/K2

Topic: C.03. Parkinson’s Disease

Support: NSTC 111－2218－E－007－019

Title: Changes in diurnal brain activity of rats with impaired dopamineric system: Implications to biomarker discovery for the Parkinson's disease.

Authors: T.-Y. YEN[1], **J. YANG**[1], Y.-H. KUO[1], Y.-C. CHANG[1], *H. CHEN[2];
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Abstract: Parkinson's Disease (PD) is one of the most common neurodegenerative diseases, affecting millions of individuals worldwide. Methodologies allowing us to detect this disease at an earlier stage and monitor its progression have been intensively investigated. High-voltage-spindle (HVSs) are spontaneous episodes of brain oscillation (5-13 Hz) which are detected in various brain areas of rodents. Increases in the frequency and power of HVSs have been reported in rats with impaired dopaminergic neurons. It has thus been proposed that increases in HVS

may be considered as an indicator of the disruption of the dopaminergic system in rodents. By utilizing a wireless neural recording system (NeuLive model F, BioProScientific), we have recorded the brain activities from multiple brain areas, continuously for 24 hours, of rats before and after their dopaminergic system is compromised, either irreversibly by 6-OH-dopamine-injection or reversibly by reserpine-injection. Our results indicate that during the course of damaging the dopaminergic system, the occurrence of HVSs in rat brain undergoes a shift in the diurnal cycle. The same set of recording data are also analyzed for the changes of other brain oscillations, including those in the regimes of high-beta and gamma, during the diurnal cycle before and after the dopaminergic system is compromised. This study introduces a novel approach to identify disease biomarkers. Traditionally, biomarkers manifest as biochemicals, behaviors, or brain signals that appear, disappear, increase, or decrease as the disease progresses. However, our findings suggest that a biomarker, such as HVS, can undergo a shift in its diurnal cycle without altering its overall level as the disease advances. These results offer valuable insights for further research and the potential discovery of non-invasive biomarkers for Parkinson's Disease.

Disclosures: **T. Yen:** A. Employment/Salary (full or part-time):; BioPro Scientific. **J. Yang:** A. Employment/Salary (full or part-time):; BioPro Scientific. **Y. Kuo:** A. Employment/Salary (full or part-time):; BioPro Scientific. **Y. Chang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioPro Scientific. **H. Chen:** A. Employment/Salary (full or part-time):; BioPro Scientific.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.09/K3

Topic: C.03. Parkinson’s Disease

Support: Michael J Fox Foundation

Title: The Effects of Chemogenetic Inhibition of Serotonin-Projecting Pathways on L-DOPA-Induced Dyskinesia and Sensorimotor Gating in a Bilateral Rat Model of Parkinson's Disease

Authors: ***N. LIPARI**[1], A. CENTNER[2], F. P. MANFREDSSON[3], K.-Y. TSENG[4], C. R. BISHOP[5];
[1]Psychology, State Univ. of New York, Binghamton, Vestal, NY; [2]Psychology, State Univ. of New York, Binghamton, Binghamton, NY; [3]Barrow Neurolog. Inst., Barrow Neurolog. Inst., Phoenix, AZ; [4]Univ. of Illinois At Chicago - Col. of Med., Univ. of Illinois At Chicago - Col. of Med., Chicago, IL; [5]Binghamton Univ., Binghamton Univ., Binghamton, NY

Abstract: Parkinson’s Disease (PD) is most commonly characterized by severe dopamine (DA) depletion within the substantia nigra (SN) leading to a myriad of motor and non-motor symptoms. The gold standard pharmacotherapy for motor symptoms Levodopa (L-DOPA), leads

to motor fluctuations like L-DOPA-induced dyskinesia (LID), and in many patients, though less understood, affective and cognitive fluctuations. One source of these fluctuations could be the raphe nuclei, wherein serotonin (5-HT) neurons possess the machinery necessary to convert and release DA from exogenous L-DOPA. In DA-depleted brain regions these 5-HT neurons can act as surrogates to the DA system and aberrant neuroplasticity which has been linked to LID may also contribute to non-motor fluctuations. In support, recent work from our lab established a positive relationship between LID and dysfunction in sensorimotor gating in parkinsonian rats treated with chronic L-DOPA implicating an underlying 5-HT mechanism. Therefore, it was hypothesized that normalizing 5-HT forebrain input would reduce the co-expression of LID and prepulse inhibition (PPI). To do so, we expressed 5-HT projection specific inhibitory designer receptor exclusively activated by designer drugs (DREADDs) using Cre-specific AAV-hM4di in tryptophan hydroxylase 2 (TPH2)-Cre, bilaterally 6-OHDA-lesioned rats. Thereafter we used of the designer drug Compound 21 (C21, 0, 3 or 6 mg/kg) to selectively inhibit 5-HT raphe-projections during L-DOPA treatment to modulate sensorimotor gating assayed by PPI and LID quantified by the abnormal involuntary movements (AIMs) test. Our results displayed that 6-OHDA bilaterally lesioned animals show significant baseline motor deficits in stepping on the forepaw adjusting steps (FAS) test compared to shams. In addition, lesion animals chronically treated with L-DOPA showed stable LID development which was significantly reduced after acute co-treatment with C21 at both doses compared to vehicle. Importantly, C21 did not significantly interfere with L-DOPA's motor efficacy once again measured using the FAS test. Our PPI data further validated previous work from our lab showing chronic L-DOPA treatment in lesioned rats produces significantly impaired sensorimotor gating compared to all other groups. Contrary to our LID effects, C21 acute co-administration with L-DOPA intensified the sensorimotor gating deficits seen in lesioned L-DOPA animals compared to C21 vehicle. Overall, this study highlighted that motor and non-motor symptoms are differentially modulated by L-DOPA and 5-HT informing novel avenues for future treatment of this heterogeneous disease.

Disclosures: **N. Lipari:** None. **A. Centner:** None. **F.P. Manfredsson:** None. **K. Tseng:** None. **C.R. Bishop:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.10/K4

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS125502

Title: The cGMP-PKG pathway signaling in striatal projection neurons for modulation of motor behavior in Parkinson's disease

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Abstract: BACKGROUND: A primary mechanism that underlies the decline of L-DOPA efficacy over the course of chronic therapy of Parkinson's disease (PD) is related to maladaptive plasticity in striatal projection neurons (SPNs). This results in altered responses to dopaminergic stimuli involving both direct and indirect SPNs (d/ i-SPNs). Dopamine responses in SPNs are mediated primarily by cAMP/Protein Kinase A and cGMP/Protein Kinase G (PKG) signaling cascades. To understand the impact of cGMP/PKG signaling on parkinsonian motor behavior, we tested the effects of PKG overexpression selectively in SPN subtypes. METHODS: We used transgenic rat lines (Cre/D1 or A2A receptors). Rats received unilateral 6-OHDA lesion of the medial forebrain bundle and apomorphine rotational test to confirm lesion extent. rAAV-Syn-Flex-PKG-GFP or scramble control virus was injected in the dorsolateral striatum in parkinsonian and intact rats. We compared the impact of increased PKG expression in either d- or i-SPNs on motor performance. We also evaluated the evolution of dyskinesia-like behaviors between groups receiving chronic L-DOPA treatment. Parkinsonian motor deficits and behavioral responses to L-DOPA were assessed before (baseline) and after virus injection using standard tests and scales. RESULTS: Elevated PKG activity in i-SPNs and d-SPNs differentially impacted motor behavior in intact and parkinsonian rats. Our results indicate that cGMP/PKG signaling plays a role in SPN responses to DA in the context of chronic PD. DISSCUSSION: Results of this study may contribute to understanding the pathophysiology of maladaptive plasticity in striatal neurons, and thereby developing new pharmacological strategies targeting SPN-specific signaling mechanisms for the therapy of PD.

Disclosures: T. Yabumoto: None. **B. Kochoian:** None. **S. Coletta:** None. **C. Bure:** None. **S.M. Papa:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.11/K5

Topic: C.03. Parkinson's Disease

Title: Sars-cov-2 infiltration of dopamine neurons suggests potential linkage to parkinson's disease

Authors: *H. CROY[1], D. THEOBALD[2], A. OMAIR[2], S. M. AKULA[2], S. SRIRAMULA[2], J. EELLS[3];
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Abstract: COVID 19 has triggered a variety of neurological ailments of which the world is just beginning to deal with. COVID-19, caused by severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2), can produce a variety of neurological symptoms such as, but not bound to, neuroinflammation, chemokine/ cytokine storms, and cognitive disorientation. These SARS-CoV-2 symptoms could exacerbate multiple neurological diseases including Parkinson's Disease (PD).PD is caused by the progressive degradation of dopamine nerve cells located in the substantia nigra pars compacta (SNpc). The SN is the region of the brain responsible for motor control and production of dopamine, in conjunction with the ventral tegmental area (VTA). A decrease in dopamine secretion is directly correlated to tremors, muscle rigidity, and impaired coordination – all hallmark PD symptoms. A link between SARS-CoV-2 and PD has been suggested, however, data is limited. One potential mechanism for SARS-CoV-2 infection damaging dopamine neurons is direct infiltration of SARS-CoV-2 into dopamine neurons located within the SNpc. To test the vulnerability of dopamine neurons to infection in vivo, the transgenic K18-hACE2 mouse model was used. The K18-hACE2 mice were infected with SARS-CoV-2 developed severe disease and were euthanized around 6 days post infection. Immunohistochemical techniques were performed on paraffin embedded brain sections and labeled for three separate fluorescent targets: [1] neural nuclei (DAPI), [2] dopamine neurons (tyrosine hydroxylase -TH), [3] SARS-CoV-2 infection (SARS spike protein). Following the immunofluorescence, slide imaging throughout the SNpc and VTA from rostral to caudal was obtained with a Keyence fluorescent microscope. Cell quantification was performed manually by transitioning between the overlay view and either the TH+ or SARS+ view of each section. Cell counts resulted in an overall SARS+TH+ infection rate of 73.3%. Interestingly, the infection rate was lower in the SN averaging 66.5% than in the VTA, averaging 79.1%. These data demonstrate that dopamine neurons are vulnerable to SARS-CoV-2 infection. Currently, the mechanism of SARS-CoV-2 infection of dopamine neurons is not known. Additionally, whether SARS-CoV-2 infects dopamine neurons in mild disease has not been determined. Future studies are underway to address this question and determine the virus's persistence in dopamine neurons along with the relevance of these potentially destructive capabilities for PD patients.

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Poster

PSTR260. Dopamine and Non-Dopamine Pathways

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Program #/Poster #: PSTR260.12/K6

Topic: C.03. Parkinson's Disease

Support: JSPS KAKENHI Grant Number JP21K07530

Title: Nt5dc2 regulates the phosphorylation of tyrosine hydroxylase

Authors: H. YAMAGUCHI[1,2], S. HARA[3], H. ICHINOSE[3], H. NAGASAKI[4], ***A. NAKASHIMA**[1];
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Med. Care, Yokkaichi Nursing and Med. Care Univ., Yokkaichi, Japan; [3]Sch. of Life Sci. and Technology, Tokyo Inst. of Technol., Yokohama, Japan; [4]Dept. Physiology, Fujita Hlth. Univ. Sch. of Med., Aichi, Japan

Abstract: 5'-Nucleotidase domain-containing protein 2 (NT5DC2) has been revealed by Genome Wide Association Studies (GWAS) as a gene implicated in neuropsychiatric disorders related to the abnormality of dopamine (DA) activity in the brain. However, it remains unknown about its physiological function, although NT5DC2 is assumed to be a member of the family of haloacid dehalogenase-type phosphatases based on only its amino acid sequence. We recently reported that tyrosine hydroxylase (TH) binds to NT5DC2 and that the down-regulation of NT5DC2 increases DOPA synthesis by increasing the level of TH phosphorylated. This result indicates that NT5DC2 could decrease in phosphorylation of TH. Therefore, we speculate that NT5DC2 has a crucial role in catecholamine biosynthesis, because TH which catalyzes the conversion of tyrosine to DOPA is the rate limiting enzyme in the biosynthesis of catecholamines and its activity is regulated by the phosphorylation of TH molecule. In this study, we examined whether the decrease in phosphorylation of TH by NT5DC2 was due to potentiation of dephosphorylation or inhibition of kinase activity. The overexpression of NT5DC2 using expression vector decreased DOPA synthesis in PC 12D cells. The decreased DOPA synthesis should be attributed to the decreased catalytic activity of TH controlled by its phosphorylation, because western blot analysis revealed that the incubation of cell lysate from PC12D cells overexpressing NT5DC2 at 37 C decreased TH phosphorylation. Next, we phosphorylated the purified TH with a kinase and then reacted the phosphorylation form of TH to purified NT5DC2. Western blot analysis revealed that purified NT5DC2 binds to the phosphorylation form of TH more than the non-phosphorylation form and that purified NT5DC2 promoted dephosphorylation of the phosphorylation form. Collectively, our results indicate that NT5DC2 decreases the DOPA synthesis by decreasing the phosphorylation of TH. We propose that NT5DC2 might regulate the phosphorylation of TH by promoting dephosphorylation like a phosphatase.

Disclosures: H. Yamaguchi: None. **S. Hara:** None. **H. Ichinose:** None. **H. Nagasaki:** None. **A. Nakashima:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.13/K7

Topic: C.03. Parkinson's Disease

Title: Distinct patterns of structural brain change progression in Parkinson's disease subtypes

Authors: *S. CRISOMIA[1], A. BOWER[2], J. CHUNG[1], R. G. BURCIU[1];
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Kinesiology and Applied Physiol., Interdisciplnary Neurosci. Grad. Program - Univ. of Delaware, Newark, DE

Abstract: Parkinson's disease (PD) is a heterogeneous neurodegenerative disease with two main motor phenotypes: tremor dominant (TD) and postural instability and gait dominant (PIGD). These phenotypes are typically distinguished based on the ratio of tremor and postural instability sub-scores on the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III). Previous studies have reported that in comparison to TD patients, PIGD patients have a faster disease progression and are more likely to develop additional non-motor symptoms. However, few studies have sought to incorporate neuroimaging to examine the differences in the rates of brain change progression between TD and PIGD sub-types. One promising progression imaging marker in PD is free water (FW). FW is a measure that assesses the presence of increased extracellular fluid in brain tissue, which is an indicator of neural degeneration and inflammation. In PD, FW imaging repeatedly demonstrated a longitudinal increase in FW in the posterior substantia nigra compared to controls that predicts changes in clinically significant measures (Burciu et al 2017, Ofori et al 2015). Our study sought to expand upon previous findings by investigating the variations in FW across multiple nuclei in the basal ganglia and cerebellar circuits between TD and PIGD patients enrolled in the Parkinson's Progression Marker Initiative (PPMI; https://www.ppmi-info.org). The cohort consisted of 18 TD and 14 PIGD patients with a similar distribution of age, sex, motor severity, and cognitive status that underwent diffusion tensor imaging at baseline and 2 years later. At baseline, TD patients had higher FW than PIGD in the subthalamic nucleus. At two years, PIGD patients showed a greater percentage increase in FW in the caudate, putamen, globus pallidus, and lobule VI of the cerebellum when compared to TD. In summary, PIGD patients showed a faster progression of structural brain changes both within and beyond the basal ganglia which may contribute to a more accelerated progression of motor symptoms as observed in the literature. These results further validate the use of FW as a marker of disease progression in PD and may allow for a better understanding of the differential disease course in PD subtypes.

Disclosures: S. Crisomia: None. **A. Bower:** None. **J. Chung:** None. **R.G. Burciu:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

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Program #/Poster #: PSTR260.14/K8

Topic: C.03. Parkinson's Disease

Support: NIH Grant MH113257

Title: High resolution histological definition in the rhesus monkey brain of fiber trajectories (ChAT, TH, and 5HT) accessing the anterior cingulum bundle

Authors: K. S. ROCKLAND[1], ***A. DUQUE**[2];
[1]Dept. of Anat. and Neurobio., Chobanian & Avedisian Sch. of Medicine, Boston Univ., Boston, MA; [2]MacBrain Resource Ctr. - Neurosci., Yale Univ. Sch. Med., New Haven, CT

Abstract: Neuromodulatory axons positive for choline acetyltransferase (ChAT), serotonin (5HT), or tyrosine hydroxylase (TH) are present in the cingulum bundle and are reported to access it by multiple routes. In order to further chart their trajectories, we visualized these at high resolution in histological sections of rhesus monkey brains reacted in spaced sequential series (1.0mm section-to-section, within the several series) by immunocytochemistry with DAB as chromogen (MacBrain Resource Center: https://macbraingallery.yale.edu/collection6/). A region of interest was delineated between the frontal pole anterior to the corpus callosum (CC) and the anterior commissure. In this material, the lateral cholinergic tract (LCT), consistent with previous reports in monkey or human brains (postmortem histology or in vivo imaging), was localized in the external capsule, but could be further differentiated as lying medial, closely adjacent to the putamen. The medial cholinergic tract (MCT) ascended in a dorsal-ventral orientation, parallel to layer 6 of the medial frontal cortex. The LCT, with anterior progression shifted medially and ventrally, and appeared to join with the MCT in a characteristic V-shaped juncture at the ventromedial edge of the anterior-most caudate nucleus or, in some brains, just anterior to this. Bundles of fibers positive for 5HT or TH followed a lateral and medial trajectory similar to that of the LCT, including the V-shaped juncture with a more medial tract. Cholinergic signal was most distinct in young brains (1 year or less), as was the V-shaped juncture (e.g., sections 17-19 in Brain 61). Fiber density was greater for TH- than ChAT-positive bundles. Scattered fibers positive for ChAT, 5HT, or TH perforated through the CC in a predominant dorsal-ventral orientation. These were especially evident near the midline at anterior levels, where they traversed between the induseum griseum, cingulum bundle, and underlying septum. In addition, there were compact bundles of fibers with an anterior-posterior orientation, evident in all three markers, that were organized in narrow striae medio-laterally oriented from the edge of the lateral ventricle; for example, see sections 18-21 in Brain 79 and section 16 in Brain 84 for all three substances, and sections 20-21 in Brain 61 for ChAT and TH. We suggest the differential fiber trajectories may be relevant for interpretation of tractography studies, and for assessing stage and progression of neurodegenerative and other disease conditions.

Disclosures: K.S. Rockland: None. **A. Duque:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.15/K9

Topic: C.03. Parkinson’s Disease

Title: Differences in VTA-SN Anticipatory Brain Responses and Positive Emotions in Parkinson's Disease.

Authors: *S. A. MABRY[1], E. RILEY[1], E. DE ROSA[1], M. GONZALEZ[1], A. K. ANDERSON[2]; [1]Cornell Univ., Ithaca, NY; [2]Dept. of Psychology, Univ. Toronto, Syracuse, NY

Abstract: Resilience, in the context of the human experience, describes being met with significant pressure but bouncing back from the stress without dysfunction or psychopathology. Experiencing positive emotions, even in stressful situations, is associated with successful adaptation and is a critical component of resilience. This study aims to compare positive emotions during stress between people living with Parkinson's disease (PD), a neurodegenerative that leads to motor and emotional changes, and healthy individuals, using a reward-effort anticipatory task. Preliminary functional MRI (fMRI) data indicates behavioral and Blood Oxygen Level-Dependent (BOLD) signal differences in the dopamine-producing Ventral Tegmental Area (VTA) and Substantia Nigra (SN) areas across groups. We hypothesize that brain activity during anticipation of trial events will differ between PD and healthy control populations and [predict behavior]. In this study, 20 participants (10 PD, 10 age-sex-education-matched healthy individuals) earn money based on their performance in a task. The maximum potential earnings are $5. Each trial consists of three phases. First, participants view a multiplier (0, 1, 10, or 100) which creates anticipation for how many points and, thus, how much money can be earned during the trial. Second, participants exert effort by pressing a button as many times as possible within three seconds to earn points. Third, participants observe the number of button presses, points, and money earned for that trial for seven seconds. Forty-eight trials are performed to determine the total points earned during the task. Behavioral data show participants with PD earn fewer points on the task than their age-sex match control (8563 vs 6400 average), press the button less often for higher reward multipliers (100,10) than healthy individuals, and may have less BOLD activation. Dopamine brain networks help people create predictions about their environment. Differences in the VTA/SN BOLD signal during reward anticipation may indicate that the SN has an understudied role in emotional processing. This role in reward, emotional processing, and resilience may explain the comorbidity between PD, depression, and compulsive disorders and the understudied progressively worsening emotional symptoms experienced by PD patients.

Disclosures: S.A. Mabry: None. **E. Riley:** None. **E. De Rosa:** None. **M. Gonzalez:** None. **A.K. Anderson:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.16/K10

Topic: C.03. Parkinson's Disease

Title: Mtorc1-s6k1-darpp32 signaling regulates homer1a expression and locomotive behavior in healthy and 6ohda lesioned mice.

Authors: *L. H. GLADULICH, R. LIN, C. S. C. REDDY, P. F. WORLEY;
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Abstract: *Homer1a* (H1a) plays an important role in synaptic plasticity, yet mechanisms that control its expression remain largely unknown. Previous work from our lab demonstrated that *Rheb*^{S16H} mutant mice, with hyperactive mTORC1, do not induce *H1a* expression in response to multiple stimuli. Additionally, we demonstrated that mTORC1-S6K1 activates DARPP32 by phosphorylation at the same site as PKA. These results suggest a link between mTORC1-S6K1-DARPP32 activity and *H1a* expression, and a role for mTORC1-DARPP32 in plasticity and behavior. To examine the role of mTORC1-S6K1-DARPP32 signaling, we generated a novel mouse model that expresses DARPP32(R29A). DARPP32(R29A) can be phosphorylated at T34 site by the canonical PKA, but not by S6K1. *DARPP32*$^{R29A/R29A}$ mice, as well as their littermate wild-type (WT) controls and *DARPP32*-KO were administered 3-5mg/kg amphetamine and their striatum was dissected after 15, 30, or 60 minutes. Tissues were analyzed by western blotting and immuno-fluorescent staining. *H1a* expression was measured via qPCR. Locomotive activation was analyzed via open field infrared recording. Additionally, cohorts of the same genotypes received unilateral injections of 6OHDA to the substantia nigra, followed by a two-week recovery time and amphetamine challenge. In response to amphetamine, we observed altered dynamic phosphorylation of ERK, mGluR5, DARPP32, S6K and S6 comparing *DARPP32*$^{R29A/R29A}$ mice with WT. Additionally, we observed a marked reduction of *H1a* expression in *DARPP32*$^{R29A/R29A}$ compared to WT and *DARPP32*-KO mice. Changes in *H1a* mRNA expression correlated with reduced localization of DARPP32 and phosphorylated histone H3 in the nucleus, suggesting their role in *H1a* expression. *DARPP32*$^{R29A/R29A}$ mice also showed diminished locomotive response to amphetamine. Lastly, 6OHDA treatment resulted in unilateral dopamine hypersensitivity in WT and *DARPP32*-KO mice that was reduced in *DARPP32*$^{R29A/R29A}$. These findings suggest mTORC1-S6K1-DARPP32 phosphorylation contributes importantly to the transcriptional induction of *H1a*. While PKA-DARPP32 appears critical for acute responses, mTORC1-S6K1-DARPP32 appears important for sustained responses and long-term adaptations.

Disclosures: L.H. Gladulich: None. **R. Lin:** None. **C.S.C. Reddy:** None. **P.F. Worley:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.17/L1

Topic: C.03. Parkinson’s Disease

Support: NIH R01-NS122226-01

Title: Effects of chemogenetic inhibition of serotonergic raphe-striatal neurons on L-DOPA-induced behaviors in a rat model of Parkinson’s Disease

Authors: *C. BUDROW[1], A. CENTNER[2], S. VENKATESH[3], M. COYLE[4], H. HOLDEN[5], F. P. MANFREDSSON[6], C. R. BISHOP[2];
[1]SUNY - Binghamton Univ. Behavioral Neurosci., Apalachin, NY; [2]Psychology, Binghamton Univ., Binghamton, NY; [3]Integrative Neurosci., Binghamton Univ., Vestal, NY; [4]Dept. of Pschology, Binghamton Univ., Binghamton, NY; [5]Binghamton Univ., Binghamton Univ., Vestal, NY; [6]Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Parkinson's disease (PD) results from the loss of dopamine (DA) producing neurons within the substantia nigra pars compacta (SNc) leading to debilitating motor impairments such as tremor, rigidity, and akinesia. DA replacement therapy via levodopa (L-DOPA), though effective, chronically can often result in the development of levodopa-induced-dyskinesia (LID), characterized by excessive hyperkinetic choreic and dystonic movements. While a myriad of mechanisms are implicated in LID, neuroplasticity within serotonin (5-HT) neurons from the dorsal raphe nucleus (DRN) appear to influence LID onset, persistence, and severity. Indeed, 5-HT cells can take up L-DOPA, convert it into DA, and release DA in an impulse-dependent manner. However, 5-HT neurons lack autoregulatory elements necessary for steady DA release and uptake, which may drive LID. While prior work has established a link between the 5-HT system and LID, a causal relationship remains elusive. Thus, the current set of experiments examined the contribution of the 5-HT system in LID progression and severity by implementing an inhibitory chemogenetic technique using designer receptors exclusively activated by designer drugs (DREADDs). In experiments 1 and 2, we virally transfected 5-HT neurons of the DRN of hemi-parkinsonian TPH2-CRE transgenic rats with inhibitory DREADDs (AAV9-hM4Di-mCherry or control AAV9-GFP) followed by chronic L-DOPA treatment. To assess the influence of DRN 5-HT inhibition on established LID, we administered the DREADD ligand C21 (0, 3 or 6 mg/kg, s.c.) in a within-subjects design in experiment 1. In experiment 2, we administered C21 (0, 0.1, 1.0 mM) directly into the DA-lesioned striatum of DRN-DREADD-transfected TPH2-CRE transgenic rats via reverse *in vivo* microdialysis to determine if local 5-HT terminal inhibition altered established LID. Results revealed C21-induced suppression of LID whether given systemically (experiment 1) or intrastriatally (experiment 2). These findings were only seen in AAV-hM4Di-expressing TPH2-CRE rats, indicating a key component of raphe-striatal functioning underlying the expression of LID.

Disclosures: C. Budrow: None. **A. Centner:** None. **S. Venkatesh:** None. **M. Coyle:** None. **H. Holden:** None. **F.P. Manfredsson:** None. **C.R. Bishop:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.18/L2

Topic: C.03. Parkinson's Disease

Support: American Parkinson Disease Association
Parkinson Association of Alabama

Title: Dynamic cell type-specific transcriptional profiles of striatal cells across theDynamic cell type-specific transcriptional profiles of striatal cells across the development of L-DOPA-induced dyskinesiadevelopment of L-DOPA-induced dyskinesia

Authors: *H. DE OLIVEIRA AMARAL[1], D. FIGGE[2], D. G. STANDAERT[3], K. L. JAUNARAJS[2];
[1]Univ. of Alabama at Birmingham Chapter, Birmingham, AL; [3]Dept. of Neurol., [2]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: L-DOPA-induced dyskinesia (LID) is a debilitating, motor side effect of L-DOPA treatment ofL-DOPA-induced dyskinesia (LID) is a debilitating, motor side effect of L-DOPA treatment of Parkinson disease (PD), precipitated by a shrinking of the therapeutic window as PD progresses and sensitization to L-DOPA develops, a phenomenon known as “priming”. A comprehensive idea of the mechanism(s) underlying L-DOPA development and stable expression have been elusive due to the heterogeneous nature of the striatum, consisting of several subpopulations of medium spiny output neurons (MSNs) and interneurons, as well as supporting cells, all of which differentially respond to L-DOPA treatment. As such the goal of the current project, was to establish a transcriptional profile of LID development and expression in each population of striatal cells, utilizing single nucleus RNA-sequencing (snRNA-seq). Mice were rendered hemiparkinsonian and treated with vehicle for 10 d or L- DOPA for 1, 5, or 10 d, corresponding with Control or Acute, Subchronic, and Chronic L- DOPA exposure, respectively. One h after the last treatment, striata was harvested from all mice and pooled into 2 separate samples/group and nuclei were isolated and purified with flow cytometry for snRNA-seq. Subsequent transcriptomic analyses revealed 28 clusters of cells, including MSNs, interneurons and glia. Subclustering of dopamine D1 receptor expressing MSNs (D1-MSNs) in both patch and matrix was particularly altered by acute experience with L-DOPA, with different subtypes being affected differentially by repeated exposure. In dopamine-depleted striata, acute L-DOPA caused a large proportion of patch and matrix D1R-MSNs to become transcriptionally active, expressing immediate early genes (IEGs) such as Fos, FosB, and Arc. Gene ontology analyses suggested that acute L-DOPA induced gene modules involved in glutamatergic synaptic function in both patch and matrix activated D1-MSNs. More chronic exposure led to enhanced transcription of genes involved in physical cellular remodeling. In addition, oligodendroglia, astrocytes, and microglia population ratios were enhanced upon L-DOPA exposure and DEG analyses revealed acute cellular activation of nearly all glial cells. These data collectively reveal a coordinated response of a majority of striatal cell subtypes to acute L-DOPA exposure that is dynamically impacted by repeated treatment and lend credence to the existence of an “engrammatic” striatal D1-MSN subpopulation that directly encodes the dyskinetic response to repeated L- DOPA treatment.

Disclosures: H. de Oliveira Amaral: None. **D. Figge:** None. **D.G. Standaert:** None. **K.L. Jaunarajs:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.19/L3

Topic: C.03. Parkinson's Disease

Support: NIMH P50MH119467
NIMH P50MH106435-06A1
NIMH R01 MH084840

Title: Double dissociation of dopamine and subthalamic nucleus manipulations on effortful cost/benefit decision making

Authors: *G. PAGNIER[1], W. F. ASAAD[2], M. J. FRANK[1];
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Abstract: Deep brain stimulation (DBS) and dopaminergic therapy (DA) are common interventions for Parkinson's disease. Both treatments typically improve patient outcomes, and both can have adverse side effects on decision making (e.g., impulsivity). Nevertheless, they are thought to act via different mechanisms within basal ganglia circuits. Here, we developed and formally evaluated their dissociable predictions within a single cost/benefit effort-based decision-making task. In the same patients, we manipulated DA medication status and subthalamic nucleus (STN) DBS status within and across sessions. Using a series of descriptive and computational modeling analyses of participant choices and their dynamics, we confirm a double dissociation: DA medication asymmetrically altered participants' sensitivities to benefits vs. effort costs of alternative choices, whereas STN DBS lowered the decision threshold of such choices without affecting cost/benefit sensitivity. To our knowledge, this is the first study to show, using a common modeling framework, a double dissociation of DA and DBS within the same participants. We compare these findings to preliminary behavioral results from an analogous effort task administered to pallidal DBS patients. As such, this work offers a comprehensive account for how different mechanisms impact decision making, and how impulsive behavior (present in DA-treated PD patients and DBS patients) may emerge from separate physiological mechanisms.

Disclosures: G. Pagnier: None. **W.F. Asaad:** None. **M.J. Frank:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.20/L4

Topic: C.03. Parkinson's Disease

Support: NSERC RGPIN - 2020-06757

Title: The influence of dopamine on afferent inhibition and corticospinal excitability

Authors: *F. C. ADAMS, S. FOGLIA, K. RAMDEO, C. V. TURCO, M. TARNOPOLSKY, A. J. NELSON;
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Abstract: Afferent inhibition is a phenomenon where the afferent volley evoked by nerve stimulation can alter the motor output assessed by transcranial magnetic stimulation (TMS) which can provide noninvasive assessments of the excitability of the sensorimotor system. This phenomenon can be elicited at two phases known as short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI). Currently, the neural mechanisms contributing to the function of these neural circuits are unclear although they are altered in special populations including Parkinson's and Alzheimer's disease. This study aimed to determine if SAI, LAI and muscle representation in M1 are modulated by dopaminergic receptor activity. In this placebo-controlled and double-anonymous study, Apo Levocarb (100mg levodopa/25mg carbidopa) and placebo were administered in two separate sessions to 32 right-handed males (mean age 24.38 ± 3.2 years). Measures of SAI, LAI and motor corticospinal maps were obtained before, at the peak plasma concentration and at the half-life following ingestion of the medication. SAI and LAI were evoked by stimulation of the median nerve and recorded from the first dorsal interosseous muscle. SAI was obtained with two interstimulus intervals (ISI) using the latency of the N20 potential: N20+2 ms and N20+4 ms. LAI was obtained using an ISI of 200 ms. Motor corticospinal maps were acquired by delivering 80 suprathreshold TMS pulses over a 6 x 6 cm grid centered over the FDI motor hotspot of the left M1. Saliva samples were obtained and a polygene score was created using the following genes: COMT, DRD2, DRD1, ANKK1, DAT1. Preliminary results indicate that SAI is modulated by dopaminergic medication. Further results are pending the completed gene analyses.

Disclosures: F.C. Adams: None. **S. Foglia:** None. **K. Ramdeo:** None. **C.V. Turco:** None. **M. Tarnopolsky:** None. **A.J. Nelson:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.21/L5

Topic: C.03. Parkinson's Disease

Title: The impact of fragile X mental retardation protein loss on nigrostriatal system vulnerability in early Parkinson's disease

Authors: *S.-L. RUMPF[1], P. GAO[1], W. CHEN[1], J. HERMS[2,3,4], T. KÖGLSPERGER[1,5];
[2]Dept. of Translational Brain Res., [1]DZNE, München, Germany; [3]Ctr. for Neuropathology and Prion Research, LMU Munich, Munich, Germany; [4]Munich Cluster for Systems Neurol. (SyNergy), Munich, Germany; [5]Dept. of Neurol., LMU Univ. Hosp., Munich, Germany

Abstract: ***Background***. In Parkinson's disease (PD), classical motor symptoms arise due to the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). The neuropathological hallmark is alpha-synuclein (α-Syn) positive inclusion bodies termed Lewy bodies (LBs), which progressively arise throughout the peripheral and central nervous system and are thought to be associated with the eventual demise of DA neurons. At the early disease stage, when Lewy body pathology (LBP) is restricted to the brainstem and olfactory bulb, is termed incidental Lewy body disease (iLBD) and can be considered to be a preclinical phase of PD. Critically, up to 20% of SNc DA neurons are already lost at this stage, despite the absence of LBP. Therefore, we aim to understand the causes of neuronal dysfunction and cell death in this early disease period. Previously we have shown that during this phase, Fragile X mental retardation protein (FMRP), an RNA-binding protein which acts as a translational repressor, is already lost from the SNc. Here, investigated molecular components of the nigrostriatal pathway in FMRP-KO mice. ***Method***. We employed female wild-type (WT, C57BL/6J) and homozygous FMRP-KO mice aged 3 months. We used immunohistochemistry (IHC) and Western blot techniques to analyse the abundance of the Dopamine Transporter (DaT), Tyrosine Hydroxylase (TH), and Dopamine receptors 1 and 2 (DRD1 and DRD2). In addition, we applied patch-clamp recording from SNc DA neurons to examine the effect of FMRP on the electrophysiological properties of these cells. ***Results***. Through quantifying IHC staining on mouse midbrain slices from either genotype, we found an increase in DaT and a decrease in TH, DRD1 and 2 in the striatum of FMRP-KO mice. Conversely, DaT, TH and DRD2 was decreased in the SNc, suggesting a region-specific effect of FMRP on midbrain integrity. Western blot data confirmed our results from IHC. Patch-clamp recordings showed no difference in basic measurements of electrical excitability (AP frequency and shape). ***Conclusion***. In summary, our study indicates a compromised nigrostriatal pathway in the absence of FMRP, further implicating FMRP in the pathophysiology of PD.

Disclosures: S. Rumpf: None. **P. Gao:** None. **W. Chen:** None. **J. Herms:** None. **T. Köglsperger:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.22/L6

Topic: C.03. Parkinson's Disease

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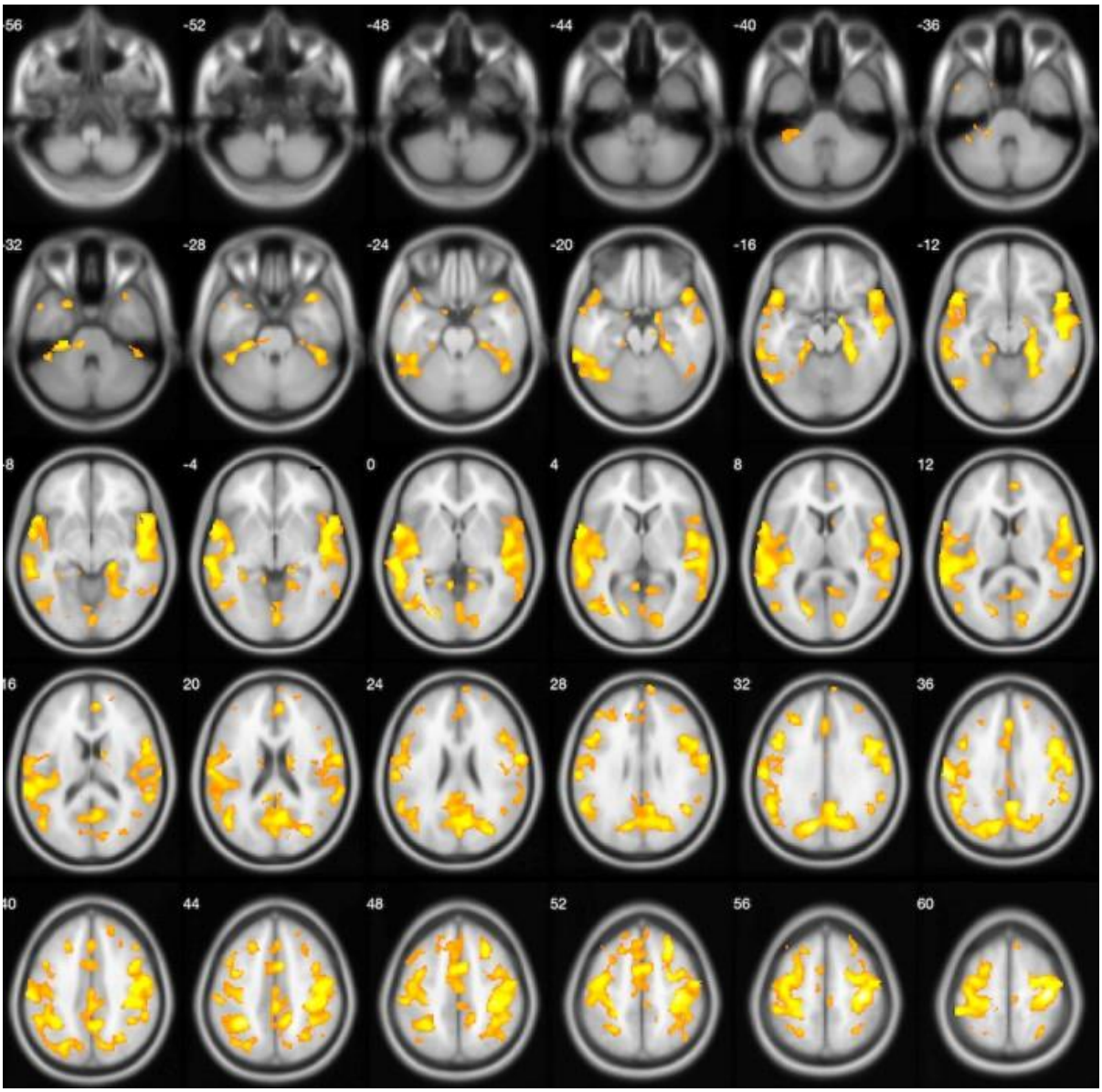
Department of Veterans Affairs (I01 RX001631)
the Michael J. Fox Foundation

Title: Topography of regional cerebral cholinergic vesicular transporter correlates of visual contrast sensitivity in Parkinson's disease: A [^{18}F]-FEOBV PET study

Authors: *P. KANEL[1], T. BROWN[1], S. ROYTMAN[1], K. A. FREY[1], P. J. H. SCOTT[1], R. A. KOEPPE[1], R. L. ALBIN[2], N. I. BOHNEN[1];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Dept Neurol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Impairments in contrast sensitivity are well documented in Parkinson's disease (PD) and have been associated with retinal dopaminergic depletion. Contrast sensitivity impairment in PD may also be predictive of cognitive decline and associated with decreased attention and visuospatial skills. The Rabin contrast sensitivity test assesses visual acuity and letter contrast sensitivity by representing different levels of contrasts in 8 lines. Here, we investigate whether contrast sensitivity is associated with cholinergic deficits in specific brain regions in individuals with PD. 113 PD subjects (88 males, 25 females; age: 66.64±6.14; disease duration: 6.15±4.68; HY: 2.42±0.53) underwent vesicular acetylcholine transporter (VAChT) [^{18}F]-fluoroethoxybenzovesamicol (FEOBV) PET and MR imaging. Rabin contrast sensitivity scores were based on incorrect answers to determine normative log contrast sensitivity values. We performed SPM whole brain voxel-based regression analysis to find clusters of spatially contiguous voxels that are statistically significant. SPM correlational analysis between Rabin scores and regional VAChT binding showed significant (FDR-adjusted $p<0.05$) reduction in the bilateral temporal poles (BA 22), insula, cingulum (posterior > anterior), right hippocampus, right lateral geniculate nucleus, right proximal optic radiation, precentral cortical, and only limited effects in the caudate nuclei and posterior visual cortical areas. Impaired contrast sensitivity was associated with cholinergic vulnerability in predominant paralimbic (BA 22, insula) and limbic (hippocampus, cingulum) regions with only limited effects in typical visual processing regions. These findings suggest that cerebral cognitive, rather than primary visual processing areas, underlie contrast sensitivity test performance. Therefore, contrast sensitivity testing may be used more as a test for cognitive performance than visual sensory assessment.



Disclosures: **P. Kanel:** None. **T. Brown:** None. **S. Roytman:** None. **K.A. Frey:** None. **P.J.H. Scott:** None. **R.A. Koeppe:** None. **R.L. Albin:** None. **N.I. Bohnen:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.23/L7

Topic: C.03. Parkinson's Disease

Support: ANR-20-CE37-0012-03

Title: Brain-heart coupling reflects the reduced motor symptoms under dopaminergic therapy in Parkinson’s disease.

Authors: *D. CANDIA-RIVERA, M. VIDAILHET, M. CHAVEZ, F. DE VICO FALLANI; Paris Brain Institute: Inst. du Cerveau, Paris, France

Abstract: Parkinson's disease (PD) is often known for its classical motor symptoms, but non-motor symptoms including autonomic dysfunctions can be much more debilitating. Autonomic dysfunctions are highly comorbid in PD and can lead to a faster motor and cognitive decline, and increased mortality risk. Noteworthy, the mechanisms behind these autonomic dysfunctions are not well understood, and it is difficult to predict the development of cardiovascular, urinary, or thermoregulatory abnormalities in these patients. During the early stages of PD, disruptions in the connectivity of multiple brain regions are observed as well. This has prompted the study of PD as a network-level phenomenon, rather than a pathology affecting specific brain regions. Our hypothesis is that by examining the relationship between brain connectivity and heartbeat dynamics, we can gain insight into the large-scale network disruptions in PD. Our results show that the coupling between brain alpha connectivity and heartbeat dynamics in PD patients is reduced, as compared to healthy participants. Furthermore, we show that PD patients under dopamine medication recover part of the brain-heart coupling, in proportion with the reduced motor symptoms, suggesting a dopaminergic-dependent physiological network. Although further research may be needed to understand the role of brain-heart communication in neurodegenerative diseases, our proposal offers a promising approach to developing new diagnostic methods for the early stages of the disease, as well as for evaluating the effectiveness of treatments.

Disclosures: D. Candia-Rivera: None. **M. Vidailhet:** None. **M. Chavez:** None. **F. de Vico Fallani:** None.

Poster

PSTR260. Dopamine and Non-Dopamine Pathways

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.24/L8

Topic: C.03. Parkinson’s Disease

Support: NIH R00MH112855
Brain Research Foundation BRFSG-2021-04
American Parkinson Disease Association R-85
Parkinson's foundation PF-IMP-867691

Title: Astrocyte calcium activity improves motor function in Parkinson's disease.

Authors: *W. R. EVANS, S. S. BASKAR, A. C. COSTA, A. ARIGBE, Z. LI, R. HUDA;
Div. of Life Sci., Rutgers Univ., New Brunswick, NJ

Abstract: The dorsal striatum is an integrative nucleus innervated by sensorimotor projections from the cortex and thalamus and is reliant on dopaminergic (DA) neuromodulation for proper functioning. Loss of DA projections into the striatum is the major cause of motor dysfunction in Parkinson's disease (PD). Though much has been learned about how diverse subtypes of striatal neurons and interneurons modulate movement, we know comparatively less about astrocyte contributions to the function of striatal circuits. In lieu of electrical excitability, astrocytes have spatiotemporally rich and robust calcium dynamics that are modulated under multiple forms of local neuronal activity. In turn, these transient increases in astrocyte calcium levels are implicated in local circuit dynamics and synaptic plasticity. Here, we studied the role of astrocyte calcium signaling in the dorsal striatum in both control and dopamine lesioned animals utilizing the 6-hydroxydopamine (6-OHDA) model of PD. We characterized the role of astrocytes in the dorsal striatal circuit by recording fiber photometry signals from mice virally expressing the membrane-tagged calcium indicator GCaMP6f-lck under an astrocyte specific gfaABC$_1$D promoter. We recorded voluntary and forced locomotion conditions in freely moving and head-fixed animals. We forced animals to locomote under two forms of DA reduction (6-OHDA and flupenthixol administration). Astrocytes in the dorsal striatum exhibit robust increases in calcium during locomotion across behavioral paradigms. Acute pharmacological dopamine receptor antagonism and chronic dopamine lesioning with 6-OHDA reduced movement-related calcium activity. To understand the behavioral effects of direct astrocyte activation, we unilaterally injected an astrocyte specific viral vector expressing either Gi-DREADD or mCherry control into the dorsal striatum and infused 6-OHDA (or vehicle) into the medial forebrain bundle (MFB). Chemogenetic activation of astrocytes in 6-OHDA lesioned animals increased open field locomotion compared to control conditions. Taken together, our data suggest that astrocytes are important endogenous neuromodulators of movement-related dorsal striatal circuits, and represent a potential therapeutic target for the motor symptoms of PD.

Disclosures: W.R. Evans: None. **S.S. Baskar:** None. **A.C. Costa:** None. **A. Arigbe:** None. **Z. Li:** None. **R. Huda:** None.

Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.01/M1

Topic: C.03. Parkinson's Disease

Support: NINDS UH3NS107709
NINDS R21 NS096398-02
Michael J. Fox Foundation (9605)
Apple Inc.
Stanford Neuroscience: Translate

Title: A unique kinematic signature of tremor in Parkinson's disease using quantitative digitography

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Abstract: *Background:* Parkinson's disease (PD) is the fastest growing neurological disease in the world. Current methods of clinical care are inefficient, requiring an in-person evaluation of motor symptoms. Quantitative Digitography (QDG) is a remote-monitoring technology that provides objective measures of all cardinal motor symptoms from a 30-second repetitive alternating finger-tapping (RAFT) task. Emergent tremor during RAFT is an involuntary movement that can overtake voluntary tapping and may contaminate measurement of motor symptoms such as bradykinesia, rigidity and freezing behavior. In this study, we developed an algorithm that reliably distinguished tremor strikes from voluntary strikes and demonstrated a unique signature of tremor during RAFT.
Methods: Ninety-six people with PD (52 males) and 42 healthy controls (20 males) participated in the study. An experienced movement disorders specialist (HBS) identified periods of tremor during RAFT from videos of trials performed by 31 tremor dominant (TD) and five akinetic rigid individuals (rater blinded to phenotype). Visually identified tremor and non-tremor strikes were used to create a labelled dataset. An XGBoost classifier was developed to identify tremor during RAFT using temporal and amplitude measures of tapping as features. The classifier's output was compared to the movement disorders specialist's (HBS) visual ratings and the time spent with tremor per trial was compared to MDS-UPDRS III tremor scores.
Results: The XGBoost classifier had 98% sensitivity, an 84.2% precision rate, a 2.7% false positive rate and a 0.981 area under the precision-recall curve. Feature importance analysis revealed that temporal and amplitude features of tapping were important for identifying tremor. The classified tremor strikes had a significantly different distribution for all temporal and amplitude metrics compared to that of non-tremor strikes. The classifier's output was consistent with the rater's visual identification for all tremor trials and four out of five trials with no tremor. The percent duration of classifier-identified tremor per trial was significantly correlated with MDS-UPDRS III tremor scores in TD participants ($P < 0.01$). QDG measures of bradykinesia, rigidity and freezing behavior from only voluntary strikes also correlated with corresponding MDS-UPDRS III items.
Conclusions: Emergent tremor during RAFT had a unique signature comprising both temporal and amplitude metrics, could be reliably measured, and was correlated with MDS-UPDRS tremor scores. Isolating tremor from voluntary tapping enabled more precise quantification of bradykinesia, rigidity, and freezing behavior.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

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Program #/Poster #: PSTR261.02/M2

Topic: C.03. Parkinson's Disease

Support: NIH NINDS R21 NS096398
Michael J. Fox Foundation (9605)

Title: Subthalamic Aperiodic Activities in Parkinson's Disease: Associations with Freezing of Gait

Authors: *C. CUI, K. WILKINS, Y.-J. GUO, R. CROCKETT, H. BRONTE-STEWART; Stanford Univ., Palo Alto, CA

Abstract: Objective: Aperiodic 1/f activity has been shown to be a physiological component of neural signals that is independent of oscillatory activity, suggesting its significance beyond mere noise. A decrease in aperiodic activity (i.e., flatter 1/f) in subthalamic nucleus (STN) local field potentials (LFP) was observed in parkinsonian compared to control rats. Additionally, lower aperiodic activity was correlated with poorer clinical motor scores in patients with Parkinson's disease (PD). However, the association between the aperiodic component and specific PD symptoms remains unexplored. The goal of this study is to investigate the association between aperiodic activity and freezing of gait (FOG), one of the most debilitating motor symptoms of PD. Methods: Seventeen PD patients (six non-freezers and eleven freezers) implanted with an investigational neurostimulator (Activa © PC + S, Medtronic PLC) were included in this study. Patients walked through the "turning and barrier course" (TBC), which we developed to elicit FOG. Patients were off medication and off stimulation. We obtained the power spectral density from STN LFPs during the TBC and extracted the aperiodic offset and exponent using the FoooF algorithm. Gait kinematics were simultaneously recorded using IMU sensors (APDM Inc.) placed on both shanks and the percentage of time spent freezing during trials was computed. Results: Preliminary data showed a significant group by STN interaction effect on the aperiodic components. Post-hoc pairwise comparisons revealed that non-freezers exhibited higher aperiodic offset and exponent in their less affected STN compared to freezers, while no difference was observed between the two groups for the more affected STN. Conclusions: Our findings suggest that PD patients who freeze may have pathologically lower aperiodic exponent across both hemispheres. We plan to further investigate this association with quantitative measures of gait impairments and explore the changes in aperiodic activity over disease progression.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Program #/Poster #: PSTR261.03/M3

Topic: C.03. Parkinson's Disease

Support: NIH NINDS UH3NS107709

Title: Beta Burst Driven Closed Loop Deep Brain Stimulation for Freezing of Gait in Parkinson's Disease

Authors: *K. WILKINS[1], E. LAMBERT[1], J. MELBOURNE[1], M. PETRUCCI[1], A. GALA[1], P. AKELLA[1], L. PARISI[1], S. ADITHAM[1], G. ORTHLIEB[1], J. A. HERRON[2], H. BRONTE-STEWART[1];
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Abstract: Background: Freezing of gait (FOG) is a debilitating symptom of Parkinson's disease (PD) that is often refractory to medication. Pathological prolonged beta bursts within the subthalamic nucleus (STN) are associated with both worse impairment and freezing behavior in PD. Both high and low frequency deep brain stimulation (DBS) improve FOG and attenuated burst durations. Therefore, the goal of the current study was to investigate the feasibility, safety, and tolerability of beta burst driven closed-loop deep brain stimulation at high and low frequencies for FOG in PD. Methods: Eight individuals with Parkinson's disease were implanted with the investigational Summit RC+S DBS system with leads placed bilaterally in the STN. A PC-in-the-loop architecture was used to adjust stimulation amplitude in real-time based on the observed beta burst durations in the STN. Patients performed either a harnessed stepping-in-place (SIP) task or a free walking turning and barrier course (TBC) OFF stimulation, on closed-loop, open-loop, or a randomized intermittent open-loop DBS. DBS conditions were performed either at high frequency (i.e., 140 Hz) or low frequency (i.e., 60 Hz). Overall motor impairment was measured as well as quantitative gait metrics across each condition. Results: Beta burst driven closed-loop DBS was successfully implemented and deemed safe and tolerable in all eight participants. Both overall motor impairment and gait metrics were improved from OFF to closed-loop DBS, which showed similar efficacy as open-loop. High-frequency DBS offered better overall symptom control compared to low-frequency DBS across all stimulation conditions. Conclusion: Beta burst driven closed-loop DBS was feasible, safe, and tolerable in individuals with PD. Less overall symptom control was observed with low frequency DBS without significant improvements in gait compared to high frequency DBS, suggesting limited generalizability of a low-frequency DBS approach.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Program #/Poster #: PSTR261.04/M4

Topic: C.03. Parkinson's Disease

Support: NIH NINDS UH3 NS107709

Title: Know your limit, rest within it: investigating the effectiveness of neural adaptive deep brain stimulation for rest tremor.

Authors: *P. AKELLA[1], R. CROCKETT[1], K. WILKINS[1], J. A. HERRON[2], H. BRONTE-STEWART[1];
[1]Stanford Univ., Palo Alto, CA; [2]Univ. of Washington, Seattle, WA

Abstract: *Background:* The Parkinsonian state is characterized by increased subthalamic nucleus (STN) neuronal oscillatory power and prolonged burst durations in the beta range (13-30 Hz). Emergence of rest tremor is associated with attenuation of STN beta activity. Neural adaptive DBS (NaDBS), driven by increased beta band power or prolonged beta burst duration is effective for treating Parkinsonian symptoms. However, it has been shown that the emergence of rest tremor during NaDBS attenuated beta band activity and caused NaDBS to decrease stimulation intensity to zero, resulting in return of Parkinsonian symptoms including tremor. We hypothesize that the use of a non-zero lower therapeutic limit (I min) for NaDBS would prevent rest tremor re-emergence. *Methods:* Four participants implanted with an investigative STN DBS system (Medtronic Summit RC+S) completed a repetitive wrist flexion-extension (rWFE) task under three stimulation conditions: 1) OFF stimulation; 2) ON NaDBS; or 3) ON open-loop DBS (olDBS), where stimulation intensity was controlled such that the total electrical energy delivered was approximately equal to that of NaDBS. The NaDBS algorithm modulated stimulation intensity within a therapeutic window (I min to I max) based on the duration of beta bursts. I min was set such that the participant received multisymptomatic benefit, including tremor, and I max was set at the maximum tolerable stimulation intensity no greater than 125% of clinical stimulation. Kinematics were recorded using IMU sensors and STN local field potentials were recorded during rest periods in the WFE task. Participant specific frequency bands for tremor were identified using the power spectral density of the gyroscopic data across an entire rest period while OFF stimulation. Tremor power was then calculated in 1 second bins using IMU gyroscopic data. Beta band power was calculated in 500ms bands in the neural timeseries between stimulation changes. Change in beta power and tremor power were compared between OFF, olDBS, and NaDBS conditions. *Results:* UPDRS-III tremor subscores decreased in the olDBS and NaDBS conditions compared to OFF DBS. On average, lower rest tremor power was observed during the olDBS and NaDBS conditions compared to OFF DBS. There was no substantial re-emergence of tremor in the NaDBS condition, even when stimulation intensity was declining. *Conclusion:* The presence of a non-zero minimum DBS intensity during NaDBS may reduce the likelihood of rest tremor re-emergence in PD. Determining safe and therapeutic DBS intensity limits in NaDBS should avoid adverse effects from over stimulation and re-emergence of symptoms from under stimulation.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Program #/Poster #: PSTR261.05/M5

Topic: C.03. Parkinson’s Disease

Support: NIH NINDS UH3 NS107709

Title: Closed loop deep brain stimulation using real-time kinematic inputs for gait impairment and freezing of gait in Parkinson's disease

Authors: *L. PARISI[1], P. AKELLA[1], E. LAMBERT[1], J. MELBOURNE[1], A. GALA[1], C. CUI[1], Y. KEHNEMOUYI[2], J. O'DAY[2], K. WILKINS[1], M. PETRUCCI[2], S. ADITHAM[1], G. ORTHLIEB[1], J. A. HERRON[3], H. BRONTE-STEWART[1];
[2]Bioengineering, [1]Stanford Univ., Palo Alto, CA; [3]Univ. of Washington, Seattle, WA

Abstract: Parkinson’s disease (PD) is a debilitating neurodegenerative disorder characterized by the cardinal symptoms of rigidity, bradykinesia, and tremor. Gait impairment (GI) and freezing of gait (GI&FOG) increase the risk of falling and negatively impact activities of daily living leading to reduced independence and quality of life. Deep brain stimulation (DBS) is an effective treatment for GI&FOG. However, standard clinical DBS uses an open loop configuration, in which stimulation settings are at a constant amplitude and frequency regardless of symptom prominence. Adaptative DBS (aDBS) can adjust stimulation parameters using real-time kinematic (K) biomarkers and may better manage symptoms by providing on-demand therapy. In this study, we used a novel KaDBS algorithm that adjusts stimulation intensity or frequency (140 Hz to 60 Hz) in response to real-time freezing behaviors, which the algorithm detects through two inertial measurement units (IMUs) placed on the patient’s shanks. The primary aim was to determine the safety and tolerability of KaDBS, and the secondary aim was to investigate changes in gait metrics in comparison to: 1) OFF DBS therapy; 2) open loop DBS (clinical settings); 3) KaDBS; and 4) intermittently adjusted DBS. Six PD participants implanted with the investigative Medtronic Summit™ RC+S system performed a harnessed stepping-in-place (SIP) task and a free walking task in a turning and barrier course (TBC) under each stimulation condition. Tolerability was assessed using aDBS custom feedback questionnaires and kinematic data from the IMUs was used to assess arrhythmicity, asymmetry, stride time, and swing angular range. Participants commonly reported no adverse effects related to stimulation changes during testing. All gait parameters improved during KaDBS compared to OFF therapy and were comparable or better than open loop and intermittent DBS. This novel KaDBS system was safe and tolerable by participants with PD and improved GI&FOG.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Topic: C.03. Parkinson's Disease

Support: NINDS Grant UH3NS103468
NINDS Grant UH3NS129898

Title: Proportional plus integral adaptive deep brain stimulation is effective at home and in clinic

Authors: *S. SCHMIDT[1], A. H. CHOWDHURY[1], K. T. MITCHELL[4], Q. GAO[2], J. J. PETERS[1], K. GENTY[4], W. M. GRILL[3], M. PAJIC[1], D. A. TURNER[5];
[1]Duke Univ., Durham, NC; [2]Duke Univ., Duke Univ., Morrisville, NC; [3]Duke Univ., Duke Univ., Durham, NC; [5]Duke Univ. Med. Ctr., [4]Duke Univ. Med. Ctr., Durham, NC

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the globus pallidus (GP) is an effective treatment for the motor symptoms of Parkinson's disease. However, patient needs from stimulation vary throughout the day based on medication and activity levels. Continuous DBS (cDBS) cannot meet the dynamic needs of patients, creating a tradeoff between side effect prevalence and symptom reduction. Patients and their neurologists select the balance between symptoms and side effects during clinic visits rather than in a naturalistic setting. Conversely, adaptive DBS (aDBS) can change stimulation parameters to respond quickly to patients' needs. However tuning aDBS settings requires specialized training and significant clinician time. Here we propose a pipeline for rapidly reducing the aDBS parameter space and demonstrate it in a cohort of 6 participants receiving dual target STN+GP DBS using the Medtronic Summit RC+S^{TM} implantable pulse generator. All study activities were approved by the FDA and Duke IRB and all participants provided informed consent.
We first determined that the amplitudes of beta (13-30 Hz) oscillations in the STN were linearly correlated to the degree of bradykinesia by measuring the speed of hand grasps. Five of six participants showed positive correlations for at least one STN and severity of bradykinesia in the contralateral hand. We then randomly varied DBS amplitude on the timescale used for aDBS to examine the range and repeatability of beta amplitudes during aDBS. These data were then used to determine initial parameters of proportional plus integral (PI) aDBS controllers. PI parameters were further refined with short experiments in clinic. In clinic there was no significant difference between unified Parkinson's Disease rating scale scores under cDBS and PI aDBS (median [inner quartile range] 20.2 [12.6 22.2] for PI aDBS; 23.2 [14, 23.9] for cDBS; $p = 0.28$ Wilcoxon signed rank). Three participants streamed data from their homes for a total of 234 hours. The participants blindly selected cDBS or PI aDBS each time streaming was started. We observed no change in tremor or dyskinesia scores while the average stimulation power was reduced with aDBS (Wilcoxon ranked sum, $p > 0.05$ for each participant's tremor and dyskinesia scores) as measured by Apple's movement disorders API. Together these data indicate that PI aDBS can

dynamically respond to changing symptom states and potentially reduce stimulation side effects in naturalistic settings. Devices were donated by Medtronic PLC.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Topic: C.03. Parkinson’s Disease

Support: NINDS Grant UH3NS103468
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NSF Grant CNS-1837499
NSF Grant CNS-2112562

Title: Deep reinforcement learning for adaptive Deep Brain Stimulation

Authors: *Q. GAO[1], S. L. SCHMIDT[1], A. H. CHOWDHURY[1], G. FENG[1], K. T. MITCHELL[1], J. J. PETERS[1], K. GENTY[1], W. M. GRILL[1], D. A. TURNER[2], M. PAJIC[1];
[1]Duke Univ., Durham, NC; [2]Duke Univ. Med. Ctr., Duke Univ. Med. Ctr., Durham, NC

Abstract: Deep brain stimulation (DBS) is a surgical treatment which delivers electrical pulses to the basal ganglia to treat motor symptoms caused by Parkinson’s disease (PD). Currently available devices deliver continuous stimulation (cDBS) at a fixed amplitude, do not adapt treatment dynamically for activity, and may cause challenging side-effects (e.g., dyskinesia). Adaptive DBS (aDBS), where stimulation parameters are modulated dynamically, has been shown effective for reducing side-effects, but existing methods rely heavily on on-site parameter tuning which requires lengthy trial and error adjustments. In this work, we introduce an offline reinforcement learning (RL) framework, allowing the use of past clinical data to train an RL control policy to adjust the stimulation amplitude in real time. The goal is to reduce energy use while maintaining the same level of treatment efficacy as cDBS, but without the need of online parameter tuning. Moreover, clinical protocols require demonstrating the safety and performance of such RL controllers prior to deployment in patients. Thus, we also introduce an offline policy evaluation (OPE) method to estimate the performance of RL control policies using historical data.

We evaluated our combined OPE-RL framework in 5 participants using the Medtronic Summit RC+S^{TM} during visits to the clinic (> 120 min per participant). Control efficacy was evaluated by severity of bradykinesia and tremor as well as participant ratings. All study activities were approved by the FDA and Duke IRB and all participants provided informed consent. The results from clinical experiments show that our RL-based controller maintains the same level of efficacy as cDBS (Wilcoxon ranked sum, $p > 0.05$ for each participant's tremor and dyskinesia scores and ratings), but with significantly reduced mean amplitude squared power (percentage reduction as proportion of cDBS; 52.2 [45.8, 58.7], 20.4 [15.9, 24.9], 12.0 [10.8, 13.3], 36.9 [34.0, 39.7], 76.9 [67.9, 85.8]; median [IQR] for each participant respectively). Further, the OPE method can accurately estimate and rank the expected returns of RL controllers, which is effective for ensuring the safety of clinical testing before deployment, as well as selecting the most promising RL controller candidate to be deployed.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Topic: C.03. Parkinson's Disease

Support: Michael J Fox Foundation
Berlin Institute of Health
German Federal Agency for Disruptive Innovation

Title: In vitro, ex vivo and clinical data from patients demonstrate that the purely thermodynamic anti-prionic mode of action for the treatment of neurodegenerative diseases is promising

Authors: *D. WILLBOLD;
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Abstract: Neurodegenerative protein-misfolding diseases, like Alzheimer's (AD) and Parkinson's disease (PD), are driven by prion-like self-replicating and propagating protein assemblies of amyloid β (Aβ), α-synuclein, and many more. The conformation these proteins have in the aggregated state is thermodynamically more stable than their physiological monomer conformation, which is often intrinsically disordered. Therefore, we have developed all-D-enantiomeric peptide ligands that bind the monomeric protein of interest with high affinity, thereby stabilizing the physiological intrinsically disordered monomer structure. These ligands are eliminating already existing aggregates by disassembling them into harmless monomers. This purely thermodynamic driven mode of action (MoA) is truly "anti-prionic", because it is

eliminating already existing oligomers and fibrils, thus disrupting prion-like replication and propagation of toxic protein aggregates.
Methods: atomic force microscopy (AFM), dynamic light scattering (DLS), size exclusion chromatography (SEC), surface plasmon resonance spectroscopy (SPR), nuclear magnetic resonance spectroscopy (NMR), and a clinical studiy: 20 AD patients in early disease stages were recruited to participate in a single center, randomized, placebo-controlled, double-blind study. Patients received once daily oral doses of 300 mg PRI-002 or placebo for 28 days.
Results: The all-D-enantiomeric ligand for α-synuclein, SVD-1a, disassembled preformed α-synuclein fibrils (PFF) as shown by AFM, DLS and SEC analysis. SPR and NMR demonstrated picomolar affinity of SVD-1a to α-synuclein monomers, while keeping them in their physiological IDP conformation. The all-D-enantiomeric ligand for Aβ, RD2, demonstrated ex vivo target engagement and disassembled Aβ oligomers obtained from brain tissue of former AD patients. A clinical phase Ib, double-bind, placebo-controlled study with 20 mild cognitively impaired (MCI) due to AD and mild AD patients treated once daily orally with RD2 or placebo for 4 weeks with an additional 4 weeks follow up period yielded good safety and tolerability. Also, as demonstrated and published before with four different animal models in four different laboratories, patients treated with RD2 improved their short term memory abilities significantly, as shown with the Word List assay of the CERAD battery of neurocognitive testing. A phase II study with 270 patients and 12 to 24 months treatment is scheduled. I will also acknowledge the many contributors of both developments that are too many to be included here in the abstract.

Disclosures: D. Willbold: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Priavoid GmbH and attyloid GmbH.

Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.09/M10

Topic: C.03. Parkinson’s Disease

Title: Optimization of Numeric Attributes for Machine Learning Distinction of an Assortment of Deep Brain Stimulation Parameter Configurations

Authors: *R. LEMOYNE[1], T. J. MASTROIANNI[2];
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Abstract: Deep brain stimulation enables an approach for resolving movement disorder symptoms, such as for Parkinson’s disease. The response to deep brain stimulation can be objectively quantified through conformal wearables comprised of inertial sensors in the context of the subject’s tremor. This inertial sensor signal data can then be consolidated to numeric attributes for distinction through machine learning of the respective deep brain stimulation parameter configurations. The amalgamation of machine learning with conformal wearable

inertial sensors enables the opportunity to produce automated diagnostics with regards to deep brain stimulation and the considerable number of available parameter configurations. Further refinement of the machine learning process can emphasize the optimization of the numeric attributes derived from the inertial sensor signal data acquired from the conformal wearables that quantify the tremor response based on the deep brain stimulation parameter configurations. The research objective is to optimize the associated numeric attributes, in order to better improve the process of achieving machine learning classification for the assortment of deep brain stimulation parameter configurations.

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Poster

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Program #/Poster #: PSTR261.10/N1

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: JST FOREST Program JPMJFR205F

Title: The behavior of the periodic and aperiodic components of LFP differ in both temporal variation and spatial distribution during the period of dissipation of the microlesion effect after deep brain stimulation electrode implantation in Parkinson's disease

Authors: *T. NAOKI[1], T. EMURA[1], Y. KIMOTO[1], T. MATSUHASHI[1], T. YAMAMOTO[3], K. HOSOMI[1], S. OSHINO[1], H. KHOO[1], Y. FUJITA[1], R. FUKUMA[2], T. YANAGISAWA[2], H. KISHIMA[1];
[1]Neurosurg., [2]Inst. for Advanced Co-Creation Studies, Osaka Univ., Suita, Japan; [3]Osaka Univ. Grad. Sch. of Med., Suita, Japan

Abstract: BackgroundB power of the subthalamic nucleus (STN) local field potential (LFP) is used as a biomarker for adaptive deep brain stimulation (DBS) therapy because it correlates with and fluctuation of the motor symptoms of Parkinson's disease (PD). However, β power is not a perfect biomarker and often does not correlate with motor symptoms. We explored the issue of β power as a biomarker by recording LFP during the 6-month period after DBS electrode implantation when the microlesion effect was wearing off.**Method**LFP was measured for 6 months in PD patients with DBS electrodes implanted in the bilateral STN and connected to a pulse generator implanted in the body. The DBS electrodes have contact numbers 0, 1, 2, and 3 in order from the ventral side. Measurements were taken at any time during outpatient visits or hospitalization, and data were later retrieved and analyzed. LFPs were transformed into power spectrum density using Fourier transform, and further divided into periodic and aperiodic components. The LFP measurement period was analyzed by dividing 6 months into 5 periods. Differences by recording period and by recording contact were statistically analyzed, respectively. Analysis was performed with the Steel-Dwass test of nonparametric multiple

comparisons, and statistical significance set at p<0.001.**Results**The subjects were 13 patients with PD, mean age at electrode implantation was 62.2 years, and the time from onset to electrode implantation was 14.5 years. The electrode contact with the highest effect on improving motor symptoms was 1 (n = 13) or 2 (n = 13). STN LFP was measured for approximately 30 seconds at a time, averaging 437 measurements per person over a 6-month. Total power increased consistently until 6 months postoperatively, as did aperiodic component. On the other hand, the periodic component increased irregularly over a six-month period. The aperiodic component tended to have a larger amplitude at the ventral contact, while the periodic component tended to have a larger amplitude at the middle contact. In particular, the periodic component of the β band tended to become progressively stronger in contact 1 and 2 during the period when the microlesion effect disappeared.**Conclusion**During the period when the microlesion effect was disappearing, the periodic and aperiodic component behaved differently and should be considered separately as biomarkers. The position where the periodic component of the β band was stronger coincided with the effective site of stimulation, which may suggest that the periodic component of the β band can be a better biomarker.

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Poster

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Program #/Poster #: PSTR261.11/N2

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Closed-loop stimulation over one year wasn't worse than conventional deep brain stimulation in advanced Parkinson's Disease patients.

Authors: *T. EMURA, N. TANI, K. HOSOMI, T. MATSUHASHI, Y. KIMOTO, M. HIRATA, H. KISHIMA;
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Abstract: It is known that the local field potential (LFP) beta band (approximately 13-30Hz) changes in correlation with fluctuation in motor symptoms of Parkinson's disease (W.-J. Neumann et al., 2017). A new deep brain stimulation (DBS) device approved in Japan in 2020 is capable of adjusting stimulation through a closed-loop system based on changes in LFP (adaptive DBS; aDBS). In addition to reducing battery consumption, aDBS is expected to reduce the duration of off-state and dyskinesia. The use of aDBS was approved for clinical use in Japan before any other country, and its safety has not yet been proven. We report our findings after introducing aDBS to our patients.We switched from conventional continuous DBS (cDBS) to aDBS in 11 Parkinson's disease patients who had undergone DBS electrode implantation and had passed more than 6 months since the surgery. PDQ39 and UPDRS were evaluated just before the

switch from cDBS to aDBS, and 6 month and 1year after the switch. UPDRS Part3 was evaluated in 4 states of stimulation on/off and medication on/off.Seven patients were male and four were female. In the nine newly implanted DBS devices cases, an average of 7.3 months had passed since electrode implantation, and in the 2 cases of battery replacement, 64 and 135 months had passed since the electrode implantation. We used PerceptTM PC of Medtronic for IPG. In 7 cases, the stimulation was effectively automatically adjusted on one side of the hemisphere. One person was not substantially automatically adjusted by the stimulation. The remaining 3 patients returned to cDBS due to side effects such as disabling dyskinesia, so aDBS was not used. For the 7 patients who continued to use aDBS, UPDRS was 58.6 points (SD 12.5) when using cDBS, 51.9 points (19.1) 6 months after using aDBS, and 59.1 points (19.6) 1 year after using aDBS. PDQ-39 was 40.8 points (21.2), 42.1 points (22.7), and 45.5 points (28.6) on average respectively. UPDRS Part 4, which is related to motor complications, was 6.0 points (2.3), 6.2 points (2.7), and 7.6 points (3.3).The fact that UPDRS improved the most after 6 months of switch to aDBS is reasonable, as this is the time when the adjustment of many parameters of stimulation is optimized. On the other hand, the original purpose of aDBS, i.e., improvement of motor complications such as dyskinesia, was not achieved. We will continue to collect and follow-up aDBS cases to clarify the usefulness of aDBS in the long term.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.12/N3

Topic: C.03. Parkinson’s Disease

Support: U19 NS110456

Title: Autoradiography validation of two novel PET radiotracers [^{3}H]M503-1619 and [^{3}H]HY-2-15 for imaging a-synuclein in PD and MSA.

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Abstract: Objective: The accumulation of aggregated α-synuclein is a pathological hallmark of Parkinson´s disease (PD) and other synucleinopathies, such as dementia with Lewy bodies and multiple system atrophy (MSA). The ability to image α-synuclein deposition in the brain would be key for the diagnosis of synucleinopathies, to monitor the disease progression over time, and to facilitate the development of novel treatments. Here within, we report the in vitro characterization of two potential radioligands for the detection of α-synuclein respectively in

Parkinson's disease and multiple system atrophy. **Methods:** For [^{3}H]M503-1619 and [^{3}H]HY-2-15 *in vitro* real-time autoradiography, fresh frozen brain sections derived from PD, PDD, MSA, AD, CBD, PSP and control cases were pre-incubated with PBS + 0.1% BSA buffer, pH 7.5 for 15 min under constant gentle shaking. Sections were then incubated for 90 min using the same buffer containing 5 nM of [^{3}H]M503-1619 and [^{3}H] HY-215 in two separate set of experiments. Non-specific binding was determined via co-incubation with 1 µM of M503-1619 and HY-2-15. Following incubation, slides were washed 2 x 5 min in ice-cold (4ºC) PBS + 20% EtOH and 1 x 1min in ice-cold dH2O, and then dried with a hot plate. Images were obtained by using the BeaQuant, a new generation of gas detector for real time autoradiography. Furthermore, immunohistochemistry studies were performed in order to investigate the nature of the autoradiographic signal. **Results:** *in vitro* real-time autoradiography experiments combined with immunohistochemistry studies revealed binding of [^{3}H]M503-1619 to α-synuclein deposits in PD brain but not in MSA; conversely [^{3}H] HY-2-15 autoradiography showed the opposite pattern. Both radiotracers were partially blocked after incubating the slides with 1µM unlabeled M503-1619 and HY-2-15, demonstrating a good selectivity of the signal. However, specific binding of both radioligands was also observed in tissue from AD, PSP, CBD cases indicating binding to tau pathology, that was confirmed by the immunostaining with ptau antibody. **Conclusions:** [^{3}H]M503-1619 demonstrates high affinity and selectivity to α-synuclein deposits found in PD brain, while [^{3}H] HY-2-15 showed the same binding pattern but in MSA pathology. These findings suggest that α-synuclein in PD and MSA has a unique conformation that is selectively recognized by the two tracers and that M503-1619 and HY-2-15 are promising candidates as imaging agents for PD and MSA.
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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.13/N4

Topic: C.03. Parkinson's Disease

Support: the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1C1C1011822)

Title: High-intensity interval training improves executive performance in early-stage Parkinson's disease patients: a preliminary intervention study

Authors: *H. SHIN[1], R. KIM[2], K. BYUN[1];
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Abstract: Exercise has been reported to be effective in improving motor symptoms in patients with Parkinson's disease (PD). However, the effects of exercise intervention on non-motor symptoms such as cognitive function are not yet well known. This preliminary study explored the effects of 6 months of moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) on the non-motor symptoms of early-stage PD patients. Thirty-three early-stage PD participants (15 males; mean age: 66 years, SD 7.8) who had been diagnosed with PD within the previous 5 years, were randomly assigned to the MICT group (n = 11), the HIIT group (n = 11), or the usual care group (UC; n = 11). Participants assigned to the MICT and the HIIT groups participated in three exercise sessions (60-80 min/session) each week for 6 months. Participants in the MICT group exercised continuously with a load equivalent to 60% of the VO_{2peak} of each individual. Participants in the HIIT group repeatedly alternated between short bouts of high-intensity cycling exercise (100 rpm, 30-50 s/bout) at 60% of their maximum aerobic power and 60 s of rest. The UC group members were directed to maintain their normal, daily physical activity levels. Before and after the exercise interventions, peak oxygen consumption and executive performance (determined based on response time (RT)/error rate (ER) for color-word matching Stroop tasks) were evaluated. VO_{2peak} of the participants in both the MICT and HIIT groups significantly increased after the 6-month exercise interventions. There was significant interaction between group (MICT, HIIT, UC) and time (Pre, Post) for Stroop RT during the incongruent task, which requires cognitive control and the involvement of related neural resources. Post-hoc results revealed that RT during the incongruent condition was significantly shortened only in the HIIT group after the 6-month intervention. Based on these results, we concluded that a long-term HIIT intervention improves the executive performance of participants in the early stage of Parkinson’s disease.

Disclosures: H. Shin: None. **R. Kim:** None. **K. Byun:** None.

Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.14/N5

Topic: C.03. Parkinson’s Disease

Support: Penn Rosemary D. Mazzatenta Scholars Award

Title: Predicting impulsivity in people with parkinson’s disease: a descriptive analysis of cohort demographics and medication usage

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Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disease worldwide, affecting up to 3% of people over the age of 65. Common treatments for PD target

dopamine, a brain neurotransmitter, and include levodopa and dopamine agonists (DA). However, DA treatment increases the risk of developing an impulse control disorder (ICD), characterized by the inability to control impulses despite self-harm. Recent work has demonstrated that a model consisting of clinical variables, DA and levodopa use, and 3 genetic markers can predict ICD risk in PD patients. How ICD risk affects different domains of human impulsivity, including response inhibition, decisional impulsivity, delayed gratification, risk-taking, and impulsive personality traits, is unknown. We first sought to characterize DA, levodopa or other PD medication exposure in people with PD who receive care at the UPenn PD clinic and are enrolled in the whole-clinic biobanking effort called the molecular integration in neurological diagnosis (MIND) initiative. At enrollment, all MIND participants self-report ICD symptoms. Next, we extracted participants' medical records to identify those who have a billing code of ICD, impulsiveness, sexual impulsiveness, or impulse disorder. We utilized descriptive statistics to summarize self-report of ICD, medication usage at time of clinical visit, and the demographics of 1475 PD individuals. Participants had an average age of 68 years old (SD = 9), 1343 (91% of total cohort) were White, 950 (64%) were male, and 525 (36%) were female. We find that only a small percentage of participants (4.36%) had an ICD diagnosis in their medical records. This differs from the self-reported frequency of 17.46% for ICD symptoms in the MIND cohort. Future research following this project involves recruiting individuals for clinical impulsivity testing to evaluate differences between high and low ICD-risk groups. The overall goal is to further validate the predictive model to enable future translation into a precision medicine treatment approach for PD patients.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.15/N6

Topic: C.03. Parkinson's Disease

Support: Medical Innovations Research Special Key Project of Shanghai 'Science and Technology Innovation Action Plan' 21Y21901100

Title: The efficacy of low-intensity pulsed ultrasound treatment in the movement disorder in Parkinson's disease: a double-blind, randomized controlled trial

Authors: *C. ZHONG[1], N. GUO[1], C. HU[2], R. NI[2], X. ZHANG[2], Z. MENG[1], T. LIU[2], S. DING[2], W. DING[3], Y. ZHAO[2], L. CAO[2], J. WU[1], Y. ZHENG[1];
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Abstract: Background Parkinson's disease (PD) is a neurodegenerative illness marked by the loss of dopaminergic neurons, causing motor symptoms. Low-intensity pulsed ultrasound (LIPUS) has been shown to improve behavioral functions in PD animal models. It is a new type of neuromodulation approach that combines noninvasiveness with high spatial precision. **Objective** To investigate the efficacy of LIPUS in the treatment of movement disorders in patients with PD. **Methods and analysis** This trial is a single-site, prospective, double-blind, randomized controlled trial. 48 participants with clinically confirmed PD at Shanghai Sixth People's Hospital were randomly allocated to one of two groups: LIPUS group or sham group in a ratio of 1:1. The LIPUS group received pulsed therapeutic US (Shanghai, China) through the temporal bone window with a frequency of 600 kHz, an intensity of 1.0 W/cm2, a duty cycle of 75% (15 ms on, 5 ms off), and a duration of 30 minutes per day for four months. The sham group provided subjects with an identical experience, but without ultrasonic waves. All of the participants continue to use pharmacological therapy as a fundamental treatment. Changes in movement disorder were compared between the LIPUS group and the sham group using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (part III) from baseline to 4 months. Additional examinations include rating scales like the Mini-Mental State Examination (MMSE), the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), as well as high-density electroencephalography (hdEEG) and functional magnetic resonance imaging (fMRI). **Results** As of June 2023, 48 subjects were enrolled; 26 have completed the study, 1 has been lost to follow-up, and 21 are receiving ultrasound treatment. The median age was 63 years old (range, 42-79 years), with 66.7% men and 33.3% women. The UPDRS III scores decreased substantially in the LIPUS group after four months of low-intensity ultrasound therapy ($df = 16$, $p=0.0022<0.05$), whereas no significant change was observed in the sham group ($df = 8$, $p > 0.05$). In addition, the BDI ($p < 0.001$) and BAI ($p = 0.004 < 0.05$) scores exhibited a similar trend with a statistically significant effect in the LIPUS group, whereas the BDI and BAI scores in the sham group decreased marginally without statistical significance. No adverse events have thus far been reported. **Conclusions** We demonstrate that LIPUS can safely, noninvasively, and effectively alleviate motor symptoms in patients with PD and improve cognitive performance, indicating the considerable potential of LIPUS as a novel neuromodulation technique for the treatment of PD.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.16/N7

Topic: C.03. Parkinson’s Disease

Support: APDA P09
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NIH/NINDS U01-NS128612
NIH/NIMH R01-MH120194
Fondazione Neurone
McDonnell Center for Systems Neuroscience

Title: Deep Brain Stimulation-Induced Local Evoked Potentials for Intraoperative Functional Mapping in Parkinson's Disease

Authors: *E. BENCE[1], W. ENGELHARDT[5], N. MANTENA[1], E. GADZIC[1], S. MIOCINOVIC[6], P. BRUNNER[5], J. T. WILLIE[5], A. HESTON[2], K. L. CHOU[2], K. CHEN[3], E. LEVIN[3,7], D. LEVENTHAL[2,8,4], E. OPRI[1];
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Abstract: Deep Brain Stimulation (DBS) is an established therapy for Parkinson's Disease (PD). Accurate surgical implantation and optimal postoperative programming require repeated testing with patient interaction, leading to discomfort and anxiety (Lee et al., 2018). Challenges remain, with up to 34% of surgeries requiring revision surgery for lead placement correction (Rolston et al., 2016). Our study aimed to determine if DBS local evoked potentials (DLEP) can guide targeting and postoperative programming. DLEPs are a recently introduced biomarker characterized by stimulation-induced oscillatory activity measured from the stimulating lead. DLEPs persist under anesthesia whereas "beta" oscillations and micro-electrode recordings (MER) require awake subjects (Schmidt et al., 2020). DLEPs could address current pitfalls by enabling asleep functional mapping, guiding postoperative programming, and minimizing patient effort. To determine the feasibility of DLEP-based functional mapping during awake surgery, we recorded intraoperative local field potentials from 18 PD subjects (STN=5, globus pallidus internus/GPi=13). We also explored the stability of DLEP features under general anesthesia (STN=3). We evaluated DLEPs evoked using low-frequency stimulation (11Hz, 0.5-3mA), and bursts of high-frequency stimulation (130Hz, 0.5-3mA). We developed a post-processing artifact-suppression pipeline to recover DLEP activity from a clinical amplifier (Neuro Omega). We also recorded spontaneous local field potential activity for peak beta power analysis (within 13-30Hz). Lead location information was recovered from imaging-based lead reconstruction. We demonstrate that our post-processing pipeline consistently extracted DLEPs during stimulation despite large stimulation-induced artifacts. Analysis of evoked responses revealed that DLEP root mean square (RMS) envelope amplitudes are highest when the stimulating contact is nearest to the sensorimotor target of the STN or GPi. We show how stimulation parameters (amplitude and frequency) modulate DLEP morphology (oscillatory frequency and amplitude), with stimuli of larger amplitudes and frequencies eliciting responses with higher amplitudes and oscillatory frequencies. The same behavior was observed in recordings from subjects who were awake as well as those who were under anesthesia. In conclusion, DLEPs have the potential to provide a data-driven approach to guide and validate electrode placement and programming within the

optimal DBS target (sensorimotor STN/GPi), and to improve the experience of patients undergoing DBS surgery.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.17/N8

Topic: C.03. Parkinson's Disease

Support: MJFF-020020

Title: The Cleveland Clinic Virtual Home Environment platform successfully provokes freezing of gait using cognitive, emotional and physical triggers on and off therapy

Authors: *M. MILLER KOOP[1], A. ROSENFELDT[4], K. SCELINA[1], L. SCELINA[1], A. S. BAZYK[4], E. KUVLIEV, Jr.[1], J. REYES TORRES[1], C. WALTZ[5], V. BERKI[1], K. HASTILOW[1], J. LIAO[1], K. B. BAKER[2], J. L. ALBERTS[3];
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Abstract: Freezing of gait (FOG) is a debilitating symptom of PD as it can lead to falls and injuries, yet effective treatment remains elusive. Deep brain stimulation (DBS) utilizing patient-specific stimulation parameters may effectively eliminate FOG episodes; however, characterizing the therapeutic effects is challenging as there is no reliable method to provoke FOG in a clinical setting. The Cleveland Clinic Virtual Home Environment (CC-VHE) utilizes an omnidirectional treadmill (Virtualizer) coupled with an immersive VR system (VIVE) that includes motion trackers to quantify gait metrics and a safety harness to prevent falling. THE CC-VHE includes three continuous walking modules that include specific triggers known to provoke FOG (1) physical, (2) cognitive or (3) emotional stress (anxiety). Four PD patients who had previously undergone surgical implantation of the Percept DBS system (> 6 months) were tested on the CC-VHE in the off antiparkinsonians medication and OFF DBS off_med-OFF_DBS) and in the on_med-OFF_DBS conditions. Medications were withheld for >12 hours and DBS was turned off at least 1 hour prior to testing. FOG episodes were identified visually in real-time and confirmed later offline with video footage by a neurologically trained physical therapist (AR). The time points of the beginning and end of FOG episodes were recorded in each video utilizing custom Matlab software. The number of FOG episodes (count) and freeze duration (s) were quantified for each trial, and Wilcoxon signed-rank tests were utilized to determine differences in outcome measures between therapy states. Three out of the four patients were able to complete all three CC-VHE modules. Across all trials, patients experienced a total

of 77 FOG episodes with a duration of 449 s. The number and duration of FOG episodes were significantly less in the on_meds-OFF_DBS compared to the off_meds-OFF_DBS condition, 49%; $p<0.05$, 54%; $p<0.05$, respectively. Patients experienced the most FOG episodes during the cognitive and physical modules, 31 for both. The CC-VHE provides a reliable, safe approach to characterizing FOG in a clinical setting as it successfully provokes numerous FOG episodes in PD patients. Although medication was able to improve FOG behavior, they were not able to resolve it completely. Future work utilizing the CC-VHE will determine if patient-specific DBS parameters can be used to eliminate FOG in PD.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.18/O1

Topic: C.03. Parkinson’s Disease

Title: Occupationally-based exercise compare well with gold standard aerobic exercises for patients with Parkinson’s Disease: A meta-synthesis

Authors: *S. AHMAD, J. K. LONGHURST, D. STILES, E. BORN, J. SHEFFLER, K. VOGEL;
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Abstract: Title: Occupationally-based exercise compare well with gold standard aerobic exercises for patients with Parkinson’s Disease: A meta-synthesis Research Question: What results in the best outcomes in Parkinson’s Disease, endurance exercise or occupation-based exercise? Methods: The subjects of the study were taken from a published Meta-analysis comparing aerobic exercise and non-aerobic exercise for Parkinson’s Disease that compared UPDRS total motor and total scores (Ahmad et. al, 2023). The meta-synthesis compared all of the activities against each other, to find any comparative advantages one may have over another. Multiple independent samples t-tests were used to compare the average unweighted effect sizes of the aerobic vs non-aerobic groups, along with comparisons of each exercise category vs. aerobic groups. A one-way ANOVA was used to compare all non-aerobic exercise groups. Placement of aerobic and non-aerobic groups was based upon the literature and Metabolic Equivalent (MET). Results: It was found that there were no significant differences between aerobic and non-aerobic exercises as a whole and their impact on PD. The aquatic group did have a slight positive difference, meaning that this option of exercise may be best for slowing the progression of motor symptoms for PD patients; more research is neededImplications: Non-aerobic eexercises may be just as effective in slowing the progression of motor symptoms in PD patients. This is important

for therapists to help their clients choose an exercise program that is significant to the patient and will encourage long term engagement.
Omar Ahmad, S., Longhurst, J., Stiles, D., Downard, L., & Martin, S. (2023). A meta-analysis of exercise intervention and the effect on Parkinson's Disease symptoms. Neuroscience letters, 801, 137162. https://doi.org/10.1016/j.neulet.2023.137162

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.19/O2

Topic: C.03. Parkinson’s Disease

Support: National Parkinson Foundation PF-SF-JFA-837334

Title: Causal evidence for the role of cognitive control networks in motor performance in Parkinson’s Disease: a combined fMRI-TMS approach

Authors: *R. PANDA[1], E. S. PROCTOR[2], Y. LI[2], Q. NGUYEN[1], R. L. ALBIN[3], M. VESIA[4], T. G. LEE[5];
[1]Psychology - Cognition and Cognitive Neurosci., [2]Psychology, Univ. of Michigan, Ann Arbor, MI; [3]Univ. of Michigan Dept. of Neurol., [4]Kinesiology, [5]Psychology, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: An accumulating body of work suggests that motor deficits in people with Parkinson’s (PwP) are driven by changes in frontal cortical processing more typically associated with executive functions such as attentional control. These changes affect the Attentional-Motor Interface (AMI), formed by interactions between attentional systems and basal ganglia circuits. Attentional systems can compensate for motor dysfunction due to dopaminergic degeneration until disease progression degrades cognitive AMI nodes, such as the dorsolateral prefrontal cortex (DLPFC), and unmasks latent motor deficits. However, the evidence from human research linking AMI disruption and motor deficits in PwP is correlational. That is, individuals with cognitive impairments often also display gait and balance deficits. In this study we perform robust causal tests of the AMI hypothesis using fMRI and a non-invasive brain stimulation technique called transcranial magnetic stimulation (TMS).
Participants initially underwent a neuroimaging session with functional magnetic resonance imaging (fMRI). Motor performance was assessed using a precision force-tracking task (FTT) while in the scanner. Participants used a grip-force dynamometer to match the movement of a cursor to the movement of a target. In half of the force-tracking blocks, participants were required to simultaneously perform a cognitively demanding 2-back working memory task to tax attentional systems. After the initial session, participants underwent three combined fMRI-TMS

sessions on separate days. Different TMS protocols were used to either focally suppress or enhance neuronal excitability in brain regions of interest. To this end, in two of the sessions participants received either continuous theta burst stimulation (cTBS) or intermittent theta burst stimulation (iTBS) over right DLPFC to transiently disrupt or upregulate activity in cognitive control networks. In the third session, participants received stimulation to a control site outside of the AMI. Immediately following stimulation, participants' motor performance was assessed inside the scanner. These sessions were counterbalanced across participants.
Dual-tasking performance resulted in increased activity in working memory and attentional networks to support motor performance. Preliminary results suggest that right DLPFC stimulation affects both tracking performance and network-level activity in the AMI relative to control stimulation. These initial results provide causal evidence for the role of the AMI in supporting motor performance in PwP.

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Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.20/O3

Topic: C.03. Parkinson's Disease

Title: Prediction of 3-year Parkinson's disease progression with Graph Based Ensemble Algorithm

Authors: J. LIAN[1], X. LUO[2], ***C. ZHANG**[3];
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Abstract: To benefit (Parkinson's disease) PD patients' disease management and treatment, we proposed a new graph-based algorithm to predict individual patients' progression from the aspects of Hoehn & Yahr (HY), Unified Parkinson's Disease Rating Scale (MDS-UPDRS) I, II, III, total score, axial score, tremor score, akinetic rigid score, Montreal Cognitive Assessment (MoCA) and Epworth sleepiness scale (ESS) on PPMI dataset.
This study analyzed a cohort consisting of 339 (PD) patients and 127 healthy controls (HC) who met specific criteria, including the availability of 3-year follow-up data, baseline genetic information, and T1 brain Magnetic resonance imaging (MRI) scans. We calculated the mean and standard deviation of label changes in the HC group and compared them to changes observed in PD patients. By establishing a reference interval based on the HC group's change values, PD patients' label scores were categorized as "no-change" if they fell within the interval or as "Better" or "Worse" if they exhibited fewer or more changes than the interval, respectively. Consequently, ten distinct three-class classification tasks were developed to predict PD progression over a 3-year period. As for graph modeling, each participant was considered a node,

with their baseline information, including tabular exams, MRI segment volumes, genetic data, and medication information as node features. Edge features were selected based on the predictive performance. An ensemble algorithm was applied for the final prediction to achieve optimal predictions utilizing the above graph models as weak classifiers.
Using our proposed algorithm, we achieved outperforming results in predicting 3-year progression for various assessments in PD individuals compared with other machine learning models. Specifically, the Micro-Average AUC values for HY, MDS-UPDRS I, MDS-UPDRS II, MDS-UPDRS III, MDS-UPDRS Total, Axial score, Tremor, Akinetic Rigid score, MoCA, and ESS were found to be 0.842, 0.681, 0.737, 0.810, 0.798, 0.775, 0.723, 0.814, 0.758, and 0.720, respectively. These results indicate that our model exhibited a high level of accuracy in prediction. Furthermore, our graph structure analysis suggested the substantial contribution of MRI and gene features to accurately predicting MDS-UPDRS II, MDS-UPDRS III, Tremor, Akinetic Rigid, MoCA, and ESS assessments.
Our proposed graph-based ensemble algorithm demonstrated impressive performance in predicting the progression of PD while also providing valuable insights through important feature analysis. Notably, objective features such as MRI and PRS (Polygenic risk scores) were helpful in predicting PD progression.

Disclosures: **J. Lian:** None. **X. Luo:** None. **C. Zhang:** None.

Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.21/O4

Topic: C.03. Parkinson’s Disease

Title: Accuracy of Medtronic Percept’s in-device battery estimate derived from clinical data following device exchanges

Authors: *E. L. HARGREAVES[1], D. L. CAPUTO[2], D. DOLCE[1], R. J. DIPAOLA[2], S. F. DANISH[1];
[1]Neurosurg., [2]Neurol., Jersey Shore Univ. Med. Ctr. (JSUMC), Neptune, NJ

Abstract: In June of 2020 Medtronic received FDA approval for its Percept PC B35200 that was released with a new built in device longevity estimate. Previously we reported findings from 35 device exchanges transitioning from the older Activa PC to the newer Percept PC. Results indicated that Percepts predicted a greater longevity of the current device over the actual previous device life of its Activa predecessor. One of the follow up questions was to determine the accuracy of the Percept estimates, which we pursue here. We retrospectively examined data from the same 35 device exchanges (09/15/2020-05/18/2022) for accuracy of the Percept estimate across session intervals in which the contact configuration and programmed parameters remained constant. Theoretically, the estimates across such an interval, should be less by the duration of the interval. The individuals were originally implanted bilaterally targeting the

subthalamic nucleus for Parkinson's. Individuals and/or sessions that did not exhibit constant programming intervals were excluded. A total of 62 interval sessions were examined, averaging 5.17 intervals/individual. The average duration of all 62 intervals was 94.39 days (1.74 sem), while the average duration of the intervals with constant programming was no different at 93.04 days (2.94 sem). A total of 13 individuals were found to have 27 intervals that met the criteria of constancy. Of the constant intervals 18/27 were deemed accurate within 30 days of actual interval (mean: 3.18 days difference; 0.68 sem) with the estimate undershooting the actual difference 13/18 times. Conversely, 9/27 of the constant intervals were inaccurate (mean: 245.17days difference; 227.87 sem; range 61-996 days) with the estimate dramatically overshooting the actual interval in all 9 instances. Of the 13 individuals, 6 exhibited consistently accurate estimates, while another 6 exhibited mixed accuracy, leaving only 1 exhibiting consistent inaccurate estimates. The 9 inaccuracies could not be accounted for by duration of estimate, number of exchanges, bipolar contact configuration, interleaving, fractionation, or duration of interval. The Medtronic Percept battery longevity estimate is accurate in a 2:1 ratio of qualifying intervals. None of the six factors examined was able to explain the 9 inaccurate estimates and the inaccuracies grossly overshot the estimate by an average of 8 months.

Disclosures: E.L. Hargreaves: None. **D.L. Caputo:** None. **D. Dolce:** None. **R.J. DiPaola:** None. **S.F. Danish:** None.

Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.22/O5

Topic: C.03. Parkinson’s Disease

Title: A randomized, placebo-controlled, double-blind, multiple ascending dose (MAD) study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of NX210c peptide in healthy elderly volunteers

Authors: D. DUMAS[1], J. LE DOUCE[2], S. MARIE[2], H. HIJMA[1], C. LACROIX[2], A. WEBER[2], S. LEMARCHANT[2], P. KREMER[1], V. BOURDÈS[2], A. I. JANUS[2], ***Y. GODFRIN**[2]; [1]The Ctr. for Human Drug Res. (CHDR), Leiden, Netherlands; [2]AXOLTIS Pharma, Lyon, France

Abstract: Background: Blood-brain barrier (BBB) dysfunction is central to aging and to the occurrence and/or progression of various neurodegenerative diseases, contributing to cognitive decline. NX210c is a synthesized 12-amino acid peptide derived from the subcommissural organ-spondin, a large brain-specific glycoprotein that contributes to neurogenesis during embryogenesis. NX210c increases BBB integrity, reduces neuroinflammation, and promotes synaptic transmission and neuroprotection (Delétage *et al*. 2021, Le Douce *et al*. 2021, Lemarchant *et al*. 2022). Therefore, NX210c is being developed as a new promising drug candidate for neurodegenerative diseases. A single ascending dose phase 1a study showed a good

safety profile and preliminary signals of effects (Bourdès *et al*. 2022) encouraging for the presented MAD study. **Objectives:** The primary objective is to assess safety and tolerability of MAD of intravenously administered NX210c (at 5 mg/kg and 10 mg/kg) in healthy elderly volunteers (HEVs). Blood pharmacokinetics (PK) is the secondary objective. Exploratory objectives aim at assessing the effects of NX210c on BBB integrity using DCE-MRI (which measures BBB permeability) and blood and cerebrospinal fluid (CSF) biomarkers, cerebral blood flow (ASL-MRI), cerebral activity (EEG, Neurocart), and neuroinflammation (blood and CSF biomarkers). **Methods:** It is a randomized, double-blind, placebo-controlled, MAD study in HEVs run in a single center in the Netherlands. Two cohorts of 15 HEVs were planned to be randomized successively (4:1 ratio), with two sentinels in each cohort. Subjects received treatment 3x/week for 4 weeks with a follow-up visit 2 weeks after last dosing. **Results:** A total of 29 subjects was randomized in 2 cohorts (cohort 5 mg/kg: 12 males, 3 females, median age 70 years-old (yo, 59-83yo, 40% >70yo); cohort 10 mg/kg: 6 males, 8 females, median age 68yo (56-91yo, 43% >70yo)). Preliminary results showed overall 51 TEAEs in 15 subjects, all of mild severity, and no serious adverse events. The most common TEAE concerned nervous system disorders (51%, headache, somnolence). NX210c half-life was 18 min on average, no accumulation was observed and mean C_{max} was 2485 and 6835 ng/mL for the cohorts at 5 and 10 mg/kg, respectively. Detailed safety, PK, and pharmacodynamic results from both cohorts will be presented further. **Conclusions:** NX210c demonstrated a good safety profile following multiple doses in healthy elderly volunteers in both doses tested. These preliminary results are very promising for further clinical development in patients suffering from neurodegenerative diseases.

Disclosures: D. Dumas: A. Employment/Salary (full or part-time):; CHDR. **J. Le Douce:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **S. Marie:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **H. Hijma:** A. Employment/Salary (full or part-time):; CHDR. **C. Lacroix:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **A. Weber:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **S. Lemarchant:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **P. Kremer:** 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.; CHDR. **V. Bourdès:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **A.I. Janus:** F. Consulting Fees (e.g., advisory boards); AXOLTIS Pharma. **Y. Godfrin:** A. Employment/Salary (full or part-time):; Axoltis Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axoltis Pharma. F. Consulting Fees (e.g., advisory boards); Godfrin Life Sciences.

Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.23/O6

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: 2E32341-23-066
2022R1A6A3A13068868

Title: Unraveling neural correlates of attention dysfunction in iRBD Patients based on a transfer learning-based explainable machine learning

Authors: *H. KIM[1], P. SEO[1], J.-S. SUNWOO[2], K.-Y. JUNG[3], K. KIM[1];
[1]Biomed. Engin., Yonsei Univ., Wonju, Korea, Republic of; [2]Dept. of Neurol., Kangbuk Samsung Hosp., Seoul, Korea, Republic of; [3]Dept. of Neurol., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: Introduction: Idiopathic rapid eye movement sleep behavior disorder (iRBD) is a precursor to neurodegenerative diseases such as dementia with Lewy bodies and Parkinson's disease. iRBD patients often exhibit cognitive deficits, especially attention dysfunction [1]. Our study examines abnormal cortical activities in iRBD patients using a transfer learning technique and a 3D convolutional neural network (CNN) classifier on single-trial EEG during a visuospatial attention task. **Methods**: We obtained 60-channel EEGs from 49 drug-naive iRBD patients and an equal number of controls during Posner's cueing task. Cortical source activity was reconstructed using weighted minimum norm estimation. Single-trial cortical activities were averaged within 50 ms timeframes, up to 800 ms. Mollweide projection displayed cortical activities on a 2D image. Input data for classification comprised 120x120x16 three-dimensional volumes (2D space x time). We proposed a transfer learning-based method to train a CNN classifier using a limited dataset and identify crucial input nodes associated with attention dysfunction in individual iRBD patients [2]. We compared this with a traditional subject-dependent approach. Leave-one-out cross-validation assessed classification performance. Layer-wise relevance propagation generated heatmaps highlighting the significance of spatiotemporal features for each iRBD patient. **Results**: The transfer learning technique achieved training accuracy of 100 ± 0.00% for both pretrained and fine-tuned classifiers, and test data evaluation accuracy of 99.81 ± 0.32%. The subject-dependent method achieved training accuracy of 99.77 ± 0.11% and test data evaluation accuracy of 65.2 ± 7.54%. Both classifiers identified the same critical input nodes for all iRBD patients. Fine-tuned classifiers identified differentiated features as crucial for each patient. **Discussion**: The subject-dependent classifier recognizes shared spatiotemporal characteristics essential for predicting the iRBD patient group, while the fine-tuned classifier identifies unique characteristics vital for predicting individual patients. These insights may inform targeted intervention strategies for cognitive impairment in iRBD patients.
[1] Massicotte-Marquez, J., et al. "Executive dysfunction and memory impairment in idiopathic REM sleep behavior disorder." Neurology 70.15 (2008): 1250-1257. [2] Kim, Hyun, et al. "Characterization of attentional event-related potential from REM sleep behavior disorder patients based on explainable machine learning." Computer Methods and Programs in Biomedicine 234 (2023): 107496.

Disclosures: H. Kim: None. **P. Seo:** None. **J. Sunwoo:** None. **K. Jung:** None. **K. Kim:** None.

Poster

PSTR261. Parkinson's Disease: Therapeutic Strategies and Clinical Interventions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.24/O7

Topic: I.06. Computation, Modeling, and Simulation

Support: Costa Healthcare Research & Design Fund (K.A. Malaga)
Swanson Fellowship in the Sciences and Engineering (K.A. Malaga)
James L.D. and Rebecca Roser Research Fund (J.R. Zak)

Title: Individualized targeting of subthalamic nucleus deep brain stimulation for gait disturbances in Parkinson disease

Authors: J. R. ZAK[1], K. L. CHOU[2,3], P. G. PATIL[2,3,4], ***K. A. MALAGA**[1];
[1]Biomed. Engin., Bucknell Univ., Lewisburg, PA; [2]Neurol., [3]Neurosurg., [4]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is effective in alleviating the motor symptoms of Parkinson disease (PD). However, a generalized targeting approach may lead to suboptimal outcomes for patients with diverse symptoms. Volume of tissue activation (VTA) modeling can be used to compute the spatial extent of stimulation relative to specific neural structures to assess clinical outcomes. Improved outcomes for gait disturbances may be obtained by stimulating regions within or around the STN. In this study, 40 PD patients who underwent bilateral STN DBS were analyzed retrospectively. The therapeutic VTA for 72 implants was calculated to quantify STN and non-STN activation in different regions. Stepwise regression was used to evaluate associations between stimulation location and improvement in gait-related outcomes (items 3.10-3.12 of the MDS-Unified Parkinson's Disease Rating Scale). Implants grouped by stimulation location were then compared in terms of symptom improvement using Kruskal-Wallis tests. Electrode position (relative to the center of the STN) was also examined for comparison. Results revealed significant positive associations between anterior STN activation and gait symptoms ($p = 0.03$ for the gait item; $p = 0.01$ for the total gait score). Significant differences in freezing of gait (FoG) ($p = 0.03$) and total gait improvement ($p = 0.02$) were also found when comparing majority anterior and majority posterior STN activation. Lastly, a significant positive association between anterior external activation and FoG ($p = 0.02$) was found for non-STN activation. In contrast, no significant relationships between electrode position and gait symptoms were found. Given these findings, anterior STN DBS may be preferable for patients whose primary symptoms include gait disturbances. Overall, this study demonstrates the utility of VTA modeling and highlights the importance of individualized targeting based on patient-specific symptoms.

Disclosures: J.R. Zak: None. **K.L. Chou:** 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 Institutes of Health, The Michael J. Fox Foundation, Parkinson Study Group, Neuraly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Wolters Kluwer, Springer Publishing. F. Consulting Fees (e.g., advisory boards); Abbott, Accordant, Advarra, Amneal, Avion, Neurocrine. **P.G. Patil:** 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 Institutes of Health, National Science Foundation. F. Consulting Fees (e.g., advisory boards); NeuroOne Medical Technologies. **K.A. Malaga:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.01/O8

Topic: C.03. Parkinson's Disease

Title: Linking Mitochondrial Localization of Oligomeric Alpha-Synuclein to TOM40 Loss and Mitochondrial Dysfunction in Parkinson's Disease

Authors: *V. VASQUEZ[1,2], J. MITRA[1], M. KODAVATI[1], J. RAO[3], M. HEGDE[1,4]; [1]Neurosurg., Houston Methodist Res. Inst., Houston, TX; [2]Neurosci., Inst. de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT AIP), Panama, Panama; [3]KL Deemed Univ., Vaddeswaram, India; [4]Med. Col., Weill Cornell, New York, NY

Abstract: Mitochondrial dysfunction, resulting from the altered function of translocases of the outer mitochondrial membrane (TOM) complex, has been associated with alpha-synuclein (α-Syn) pathology in Parkinson's disease (PD). However, the specific mechanism by which α-Syn accumulation drives the depletion of TOM40, a key component of the TOM complex, is not well-understood. In this study, we demonstrate that the loss of TOM40 in PD patients' brains involves protein degradation triggered by the mitochondrial localization of α-Syn. Experiments using α-Syn mutants with and without mitochondrial targeting sequences (MTS) in neuron cultures confirm this. Furthermore, we observed that factors such as 6-hydroxy dopamine and oxidative stress, which promote α-Syn oligomerization, significantly expedite TOM40 depletion in PD patient-derived cells carrying the SNCA gene triplication. Our data show that α-Syn interacts with both TOM40 and TOM20 in the outer mitochondrial membrane but leads to the depletion of only TOM40 via the ubiquitin proteasomal system (UPS) pathway. Detailed investigations, including Seahorse metabolic analysis, electron microscopy, mtDNA sequencing, and damage assessment, revealed that the mutant α-Syn-induced TOM40 loss results in compromised mitochondrial function characterized by reduced membrane potential, increased mtDNA damage, mutations, and morphological alterations. These findings provide critical insights into the relationship between
α-Syn accumulation, TOM40 degradation, and mitochondrial dysfunction, offering potential avenues for targeted interventions to mitigate mitochondrial defects in PD.

Disclosures: V. Vasquez: None. **J. Mitra:** None. **M. Kodavati:** None. **J. Rao:** None. **M. Hegde:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.02/P1

Topic: C.03. Parkinson's Disease

Title: Determining Parkinson's Disease-causing variants in Parkin using a pooled FACS-based screen

Authors: *A. J. GILSRUD, J. A. THAYER, D. P. NARENDRA;
NINDS, NIH, Bethesda, MD

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's Disease. The characteristic motor symptoms in PD are due to degeneration of dopamine neurons within a region of the midbrain called the substantia nigra pars compacta. Approximately 500,000 Americans are diagnosed with PD. 5-10% of Parkinson's disease cases are caused by genetic mutations, with loss of function mutations in PRKN (coding for the protein Parkin) being the most common cause of autosomal recessive Parkinson's disease. The pathogenicity of many PRKN missense variants, however, remains unknown. We recently found that approximately 1% of individuals carry a rare PRKN missense variant of unknown significance, complicating genetic counselling (Zhu et al. 2022). To resolve this uncertainty, we generated a pooled cDNA library of all rare Parkin missense variants in publicly available databases as well as alanine substitutions of critical Parkin residues (599 variants in total). The Parkin variants in the library were additionally tagged with YFP. Finally, we developed a novel FACS based screening approach to resolve the functional status of each variant, using two single-cell reporters of Parkin function we sorted cells into pools and utilized a next-generation sequencing approach to differentiate benign mutations from loss of function mutations. From our initial screens five novel loss of function mutations have been identified. Using pooled mutagenesis, we are constructing smaller libraries of the 599 variants to obtain full coverage from the FACS-based screens. The structural relationship of variants identified by subsequent screens will be assessed by mapping them onto the solved structures of Parkin in its auto-inhibited and active states. We anticipate the results of this study will help resolve the functional consequence of PRKN variants in the population and additionally reveal novel structural requirements for Parkin activity.

Disclosures: **A.J. Gilsrud:** None. **J.A. Thayer:** None. **D.P. Narendra:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.03/P2

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS R21 NS121959-01A1

Title: An adeno-associated virus (AAV)-based tool to specifically damage mtDNA in astrocytes within pre-specified regions of the adult mouse brain

Authors: *D. A. AYALA, A. J. MATARAZZO, B. SEABERG, M. RIMER, R. SRINIVASAN; Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Astrocyte Ca2+ signals are important for neuronal function. We have shown that astrocytes in live dorsolateral striatum (DLS) slices exhibit robust spontaneous Ca2+ influx events in their mitochondria, suggesting that astrocyte mitochondria actively participate in neuronal function. Based on this rationale, we hypothesize that the specific disruption of mitochondrial function in astrocytes within pre-specified brain regions would manifest as neuronal dysfunction in that brain region, while also accelerating neurodegeneration. To damage astrocytic mitochondria in pre-specified brain regions, we created an AAV expressing the restriction enzyme PstI (Mito-PstI) under the astrocyte GCaMP6f promoter and a Mito7 signal sequence. In principle, this AAV, Mito-Pst1, can direct AAV-expressed Pst1 specifically to astrocytic mitochondria. We rationalized that since mice possess Pst1 restriction sites in their mitochondrial DNA (mtDNA), flanking genes involved in the mitochondrial oxidative phosphorylation cascade, the AAV-mediated expression of Pst1 only in astrocytic mitochondria would significantly damage mtDNA in astrocytes. We also created a control AAV expressing GFP targeted to astrocytic mitochondria (called Mito-GFP). Mito-PstI and Mito-GFP were co-injected into the dorsolateral striatum (DLS) of mice, a brain region relevant to Parkinson's disease. Compared with control mice injected with only Mito-GFP, in mice injected with Mito-PstI, we observed a significant depletion in mtDNA content and a specific deletion of the PstI-flanked mtDNA sequence. Mito-PstI demonstrated a significant increase in the number of mitochondria, a decrease in mitochondrial size, and altered mitochondrial network structure in DLS astrocytes. Mito-PstI also caused significant changes in inflammatory profiles within the DLS and increased astrocytic GFAP and microglial IBA1. Functionally, the kinetics of spontaneous mitochondrial Ca2+ influx signals in Mito-PstI expressing astrocytes was significantly altered. We also found that exposure of Mito-Pst1 expressing DLS astrocytes to the mitochondrial decoupler FCCP caused a substantial increase in the production of reactive oxygen species in DLS astrocytes as well as a delay in the loss of TMRM fluorescence as a measure of loss of mitochondrial membrane potential. Together, these data show that we have successfully developed an AAV-based tool to specifically damage mtDNA in astrocytes in predetermined brain regions. In the future, we will use this tool to study the acceleration of neurodegeneration in the context of Parkinson's disease.
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Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.04/P3

Topic: C.03. Parkinson's Disease

Support: NS123405

Title: Repair of ATP synthase stoichiometry rescues neurite outgrowth defects in DJ-1 lacking mesDA neurons

Authors: *R. CHEN[1], P. LICZNERSKI[1], C. MARTINEZ-ACEVES[1], W. CARTER[1], M. GRAHAM[1], W. MANDEMAKERS[2], V. BONIFATI[2], E. A. JONAS[1];
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Abstract: Mitochondrial dysfunction is a hallmark of the development of PD. Fibroblast studies can provide a way to detect pathological alterations present in brain. In comparing the mitochondrial properties (morphology and bioenergetics) of fibroblasts containing mutant DJ-1 to those of aged-matched healthy controls or to patient cells lacking DJ-1, we observed that average mitochondrial electron density in fibroblasts that lack DJ-1 completely is greater than that of the healthy controls or of cells containing mutant DJ-1, suggesting that there is a different metabolic condition present in cells completely lacking DJ-1. Both sets of PD patient fibroblast mitochondria carry dramatically low numbers of cristae; in addition, we also noticed that fibroblasts containing mutant or lacking DJ-1 have much lower overall protein synthesis rate than the control group. Protein synthesis rates in these cells were normalized by overexpression of the ATP synthase β subunit, which enhances mitochondrial inner membrane coupling. We used DJ-1-/- neurons as a model for the patient neurons lacking DJ-1. We measured protein synthesis rate for ATP synthase β subunit by puromycin proximity ligation assay (PLA). During four weeks of growth, the DJ-1-/- neurons had a lower rate of β subunit protein production than the WT neurons, especially at the 3rd week, when neurite growth is most exuberant. The low level of ATP synthase β-subunit protein could also result from low β-subunit mRNA, therefore we speculated that the mechanism of decreased growth and branching of DJ-1 deficient neurons is likely related to a lack of DJ-1 trafficking of mRNAs to distal neurites. As we expected, our data showed that the ATP synthase β-subunit mRNA levels are strikingly low in DJ-1-/- neuronal processes.To confirm our hypothesis, we introduced exogenous ATP synthase β-subunit in DJ-1-/- cortical neurons or TH+ neurons. We found that the defects of the total protein synthesis rate in these neurons were completely recovered, and the defects of TH + neuronal outgrowth were significantly improved. These observations suggest a connection between ATP synthase complex stoichiometry, protein synthesis rate and PD.

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Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.05/P4

Topic: C.03. Parkinson's Disease

Support: National Research Foundation of Republic of Korea (2018R1D1A3B07047960)
BK21 program by National Research Foundation of Republic of Korea
Soonchunhyang University Research Fund

Title: Nox4 plays an essential role in mediated neuroinflammatory cytokines in the hippocampal astrocytes of Parkinson's disease

Authors: C. KIM[1], *S. YI[2];
[1]Dept. of Med. Sci., Soonchunhyang Univ., Asan, Korea, Republic of; [2]Dept. of Biomed. Lab. Sci., SoonChunHyang Univ., Asan, Korea, Republic of

Abstract: Oxidative stress and mitochondrial dysfunction have been believed to play an important role in the pathogenesis of aging and neurodegenerative diseases, including Parkinson's disease (PD). The excess of reactive oxygen species (ROS) increases with age and causes a redox imbalance, which contributes to the neurotoxicity of PD. Accumulating evidence suggests that NADPH oxidase (NOX)-derived ROS, especially NOX4, belong to the NOX family and is one of the major isoforms expressed in the central nervous system (CNS), associated with the progression of PD. We have previously shown that NOX4 activation regulates ferroptosis via astrocytic mitochondrial dysfunction at the Alzheimer's disease. At present, there are limited data to understand the molecular mechanism of whether NOX4 regulates the pathogenesis of PD. This study was designed to evaluate if NOX4 is involved in PD by MPTP-induced PD mouse model compared to human PD patients. We could detect that the hippocampus was dominantly associated with elevated levels of NOX4 and α-synuclein during PD and the neuroinflammatory cytokines, myeloperoxidase (MPO) and osteopontin (OPN), were upregulated particularly in astrocytes. Intriguingly, NOX4 suggested a direct intercorrelation with MPO and OPN in the hippocampus. Upregulation of MPO and OPN induces mitochondrial dysfunction by suppressing five protein complexes in the mitochondrial electron transport system (ETC) and increases the level of 4-HNE leading to ferroptosis in human astrocytes. Overall, our findings indicate that the elevation of NOX4 cooperated with the MPO and OPN inflammatory cytokines through mitochondrial aberration in hippocampal astrocytes during PD.

Disclosures: C. Kim: None. **S. Yi:** A. Employment/Salary (full or part-time):; BK21 Program, Department of Medical Science. 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 Research Foundation of Republic of Korea (2018R1D1A3B07047960), and Soonchunhyang University Research Fund. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Human Parkinson's disease tissues were gifted from the Netherlands Brain Bank..

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.06/P5

Topic: C.03. Parkinson's Disease

Support: DOD Grant W81XWH-21-1-0908

Title: Usp13 role in parkin stability and function in parkinson's disease

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Abstract: PINK1 along with parkin is known to play a key role in mitophagy control. However, dysfunction of PINK1/parkin-dependent mitophagy is attributed to pathogenesis of Parkinson's Disease (PD). Parkin is a cytosolic E3 ubiquitin ligase that mediates mono/poly-ubiquitination of itself and of several diverse target proteins (AIMP2 and PARIS). Parkin gets mutated in autosomal recessive and sporadic early-onset PD. Mitochondria damage mediates activation of parkin-dependent mitophagy pathway. Nevertheless, substantial evidence also justifies that along with ubiquitination, deubiquitination process is also important in regulation of protein stability and signaling in mitophagy. This process is catalyzed by a large group of deubiquitinating enzymes (DUBs) known as ubiquitin-specific proteases (USPs). USPs have three major regulatory mechanisms: post-translational modifications, allosteric interactions, and subcellular localization. Furthermore, it is yet to be investigated whether USP13 regulates the stability and function of parkin. Under oxidative stress conditions, it has been reported that parkin protein levels are reduced, even though its mRNA levels are upregulated. However, it is not known what mechanism causes a discrepancy between the mRNA and protein levels of parkin in response to oxidative stress. Our experiment results showed the USP13 interaction with parkin under basal conditions using tandem affinity purification (TAP) coupled with mass spectrometry in SH-SY5Y cells expressing TAP-tagged parkin. Further, we found USP13 responsible for regulating the stability and function of parkin under basal condition as a deubiquitinase of parkin that confirmed through some experiments **(i)** downregulation of USP13 and Parkin mRNA and protein expression under oxidative stress conditions in SHSY-5Y cells **(ii)** USP13 deubiquitinates the ubiquitinated Parkin under basal conditions of hemagglutinin (HA)-Ub overexpression in HEK-293 cells **(iii)** USP13 regulates basal parkin stability via ubiquitin-proteasome pathway in SHSY-5Y cells **(iv)** USP13 depletion leads to parkin downregulation and its substrates accumulation studied in SHSY-5Y cells. Also, when oxidative stress is induced by 6-hydroxydopamine, USP13 regulates parkin through the ubiquitin-proteasome pathway and parkin functions downstream of USP13 in the regulation of cell viability. Further, clinical relevance was established when USP13 and Parkin protein expression levels were found reduced in PD brains. Our results clearly indicate that maintenance of USP13-parkin pathway could be critical for mitochondrial function and cellular defense in PD pathological conditions.

Disclosures: **M. Kwatra:** None. **J. Park:** None. **Y. Lee:** None. **H. Ko:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.07/P7

Topic: C.03. Parkinson's Disease

Support: DFG ME1922/17-1

Title: Mitochondrial CISD1 is a downstream target that mediates PINK1 and Parkin loss-of-function phenotypes

Authors: *A. METHNER[1], S. BITAR[2], L. ZHANG[2], G. ARENA[3];
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Abstract: Parkinson's disease (PD) is caused by progressive degeneration of dopaminergic neurons in the substantia nigra of the midbrain. Mutations of the kinase PINK1 and the ubiquitin ligase Parkin, proteins involved in mitochondrial quality control, cause familial PD. The homodimeric mitochondrial iron-sulfur-binding protein CISD1 is a major target of Parkin-mediated ubiquitination and loss of CISD1 is associated with mitochondrial dysfunction, an altered redox state, and iron accumulation, which are also all hallmarks of PD. To ask if CISD1 is an important player in PD, we studied its role in Pink1 and Parkin mutant flies, dopaminergic neurons from patients suffering from PINK1 mutation, and fibroblasts without CISD1 or with a CISD1 mutant lacking its iron/sulfur cluster. Loss of Cisd, the Drosophila orthologue of CISD1, rescued the detrimental effects of Pink1 loss of function on lifespan, wing posture, climbing ability and mitochondrial ultrastructure. Gene reduction of Cisd also rescued Parkin-mediated defects in climbing ability and lifespan. Pink1 mutant flies and patient-derived dopaminergic neurons had a higher propensity to form CISD1 dimers. This corresponds to the iron-depleted state of CISD1 and a CISD1 mutant incapable of binding the iron-sulfur cluster results in mitochondrial fragmentation and increased levels of reactive oxygen species.Our results from both flies and humans suggest that the mitochondrial iron-sulfur cluster protein Cisd is downstream of the cascade initiated by Pink1 and Prkn loss of function. This sheds light on the pathophysiology of familiar and possibly also sporadic Parkinson's disease and implicates CISD1 as a therapeutic target protein.

Disclosures: A. Methner: None. **S. Bitar:** None. **L. Zhang:** None. **G. Arena:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.08/P8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2021R1A2C1005469

Title: Ubiquitin-proteasome system and autophagy-lysosomal pathway affect each other during two neurotoxin-mediated differential cell death events in dopaminergic MN9D cells

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Abstract: The accumulation of misfolded or damaged proteins is a key pathogenic mechanism in many neurodegenerative disorders, including Parkinson's disease (PD). Thus, elucidating the precise operation and regulation of two intracellular proteolysis system such as ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathway (ALP) is very important. Although many studies have suggested a close link between the UPS and ALP in resting cells, their interplay and tight regulation have rarely been studied during neuronal cell death. In this study, we explored whether and how the UPS and ALP affect each other in two neurotoxin-based cell death models of PD. Previously studies showed that dysregulated autophagy contributes to caspase-dependent neuronal apoptosis in dopaminergic MN9D cells by 6-hydroxydopamine (6-OHDA), whereas autophagic malfunction caused by 1-methyl-4-phenylpyridinium (MPP^+) treatment was due to impaired autophagic degradation associated with lysosomal deficits. In this study, monitoring intracellular UPS and ALP activity using their specific reporter plasmids revealed that treatment of MPP^+ or 6-OHDA decreased proteasome activity in MN9D cells. In addition, when the cells were co-treated with each toxin plus the ALP inhibitor ammonium chloride, the inhibition of ALP relieved the 6-OHDA-induced reduction of proteasome activity, whereas MPP^+-induced proteasomal inhibition was substantially potentiated. Moreover, when the cells were co-treated with each toxin plus the proteasome inhibitor MG132, 6-OHDA-induced excessive autophagic flux was considerably promoted, whereas the MPP^+-induced impaired autophagy activity was alleviated via autophagy induction. Taken together, these findings suggest a dynamic interplay between the UPS and ALP operating in MN9D cells, which affect each other under two distinct toxin-mediated cell death pathways. This novel perspective can be developed as a potentially effective strategy for PD treatment.

Disclosures: **J. Park:** None. **H. Jang:** None. **H. Rhim:** None. **K. Chung:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.09/P9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Assessment of GPNMB as a lysosomal dysfunction biomarker in a chronic CBE-treated mouse model.

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Abstract: Some neuronopathic diseases can be described as lysosome dysfunction or lysosomal storage disorders (LSD) causing the accumulation of lipid glycoproteins tied with lysosomal degradation. One example is Gaucher's Disease (nGD)-- specifically type 2 and 3. It is characterized by a GBA1 gene mutation that encodes for a lysosomal hydrolase named acid B-glucosidase (GCase). This same gene has been associated with an increased Parkinson's Disease risk (PD) in humans. Mutations in the GBA1 gene and the lack of GCase activity result in the accumulation of glucosylceramide (GlcCer) —a glycolipid found within lysosomes and macrophages. In an effort to study nGD, two transgenic mouse models have been investigated ($Gba^{flox/flox}$ and K14-lnl/lnl); however, these strains are not ideal given their short lifespans, severity of disease, and cost. An alternative to transgenic mice, is the use of the chemical, conduritol B-epoxide (CBE) as an irreversible inhibitor of GCase activity. Chronic administration of this drug has been used to represent GD in mouse studies. Literature reports (mice) show the use of CBE inhibits GCase activity, increases GlcCer levels in brain, and changes GPNMB levels in CSF. Given this information, we sought to repeat these findings using chronic CBE (21 days) treatment (N=6, 50, 100 mpk) in female C57Bl6 mice (9 wks.) and measure multiple readouts for LSD induction. Some results following chronic CBE included the following: 1) GCase activity is significantly decreased at doses of 50 and 100 mpk in both mouse frontal cortex and hippocampus (34-66%) compared to controls; 2) brain levels of GPNMB significantly increase following 100 mpk CBE treatment in mid-cortex and hippocampus (50-97%); and 3) similar to brain GPNMB increases, levels of RNA expression in mouse cortex increased dramatically compared to controls (3 - 100 fold). Taken together, these data and others both corroborate and support previous literature reports detailing GPNMB as a marker of lysosomal dysfunction--warranting further evaluation as a biomarker in neurological diseases such as nGD and PD.

Disclosures: **F.D. Tingley:** A. Employment/Salary (full or part-time):; Eli Lilly & Co.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eli Lilly & Co. **M.G. Schmitt:** A. Employment/Salary (full or part-time):; Eli Lilly & Co.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eli Lilly & Co. **B.A. Jenkins:** A. Employment/Salary (full or part-time):; Eli Lilly & Co.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eli Lilly & Co. **R. Raghunathan:** A. Employment/Salary (full or part-time):; Prevail Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Prevail Therapeutics. **H. Wang:** A. Employment/Salary (full or part-time):; Eli Lilly & Co.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eli Lilly & Co..

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.10/P10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Molecular Signaling Pathway in Manganese-Induced Apoptosis

Authors: *K. PRABHAKARAN[1], N. K. GUNASEKARAN[2], A. SERGEON[1], G. T. RAMESH[1], J. C. HALL[3];
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Abstract: Exposure to high levels of manganese (Mn) has been shown to cause a Parkinson's-like syndrome known as manganism. Although much is known concerning the essentiality and toxicity of manganese, the mechanism for the neurodegenerative damage specific to select brain regions is not clearly understood. Hypoxia-inducible factor-1 α (HIF-1 α) is a transcriptive factor that regulates genes involved in metabolism, angiogenesis, proliferation, and apoptosis. HIF-1 α can respond to hypoxic and a variety of non-hypoxic stimuli that can initiate Reactive Oxygen Species (ROS) production, which then can activate the HIF-1 α cascade. In this study, an immortalized dopaminergic cell line was used to characterize the cell death signaling cascade activated by Mn. Mn-treated cells exhibited concentration-dependent apoptosis that was caspase-dependent and induced a dose-dependent increase of HIF-1 alpha expression, paralleling the cell death response. Mn induced a rapid surge of intracellular reactive oxygen species (ROS) generation, followed by p38 mitogen-activated protein kinase (MAPK) activation that leads to nuclear accumulation of hypoxia-inducible factor-1alpha (HIF-1alpha). Activation of p38 MAPK and HIF-1alpha accumulation were attenuated by N-acetyl-L-cysteine, GSH (antioxidants), 1400W (specific iNOS inhibitor), or a selective p38 MAPK inhibitor (SB203580), showing that oxidative stress and p38 MAPK act as upstream signals in the induction of HIF-1 alpha. Finally, RNAi knockdown of HIF-1 alpha protected the cells from Mn-induced mitochondrial dysfunction and cell death. These results indicate that Mn activated the HIF-1alpha-mediated signaling pathway, which served as an initiator of Mn-induced apoptosis in neuronal cells.

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Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.11/Q1

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Science Centre Sonata Bis grant no. 2018/30/E/NZ1/00144
ESF, POWR.03.02.00-00-I028/17-00.

Title: Striatal arginase 2 supports functioning of mitochondria

Authors: *M. PODGAJNA[1], A. OWCZAREK[1], A. DALKA[1], A. KACZYNSKA[1], K. SKOWRONSKA[2], M. ZIELINSKA[2], M. WEGRZYNOWICZ[1];
[1]Lab. of Mol. Basis of Neurodegeneration, [2]Dept. of Neurotoxicology, Mossakowski Med. Res. Inst. Polish Acad. of Sci., Warsaw, Poland

Abstract: Arginase converts arginine (Arg) to ornithine (Orn). Arg2 appears to be the only arginase isoform in resting brain, although its distribution is limited to only few subpopulations of brain cells. Striatum is strongly enriched with Arg2, but the role and exact localization of this protein is unknown. Here, we aimed at determining detailed Arg2 localization and establishing the importance of Arg2 for Arg homeostasis and cellular pathways in striatum. We used in our experiments 3-months-old control WT C57Bl/6J mice and genetic model of Arg2 loss (Arg2 KO mice; Arg2tm1Weo/J), both males and females. We used western blot for measurements of protein levels and immunohistochemistry for analysis of protein localization. We have confirmed that Arg2 has been is the only arginase isoform expressed in the striatum under physiological conditions. As expected it localized in the mitochondria, was absent in microglia and astrocytes, but was specific for medium spiny neurons (MSNs),- where it was found primarily in cell bodies. To analyze Arg-related metabolic pathways controlled by Arg2 in striatum, we compared C57 and Arg2 KO mice for their amino acid profiles (HPLC, n=10-13), polyamine levels (MS) and nitrates and nitrites content (NOx as a cellular measure of nitric oxide (NO)) and α-ketoglutarate levels (n=6). We have found that loss of Arg2 resulted in a significant accumulation of Arg ($p > 0.004$) in the striatum, but didn't affect any other measured parameter. Then we performed proteomic study (n=5) which indicated that loss of Arg2 results in changes in the expression of several mitochondrial proteins, including some components of respiratory chain. Summarizing, Arg2 in the striatum is restricted to MSNs, suggesting its specific role for these neuron functioning. Arg2 controls Arg levels, but its absence does not affect ornithine (Orn) content, what may suggest activation of compensatory mechanisms to maintain Orn bioavailability. Importantly we show that Arg2 doesn't affect NOx content, what negates the hypothesis that Arg2 is a negative regulator of NO synthesis by competing with NOS for their common substrate, Arg (at least in resting brain, where NOS activity is low). The results of the proteomic analysis suggest that Arg2 may support proper functioning of striatal mitochondria and impairment of this enzyme, that was observed in Huntington's disease model (Bichell et al., 2017), may contribute to the development of the disease.

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Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.12/Q2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH-NINDS (R01 NS065808)
NIH-NINDS (R01 NS127403)
Legacy of Angels Foundation
European Leukodystrophy Association

Title: Mechanisms of synaptic death in lysosomal storage diseases

Authors: *D. ZELADA, N. SALDIVIA, A. KONJETI, R. REBIAI, M. I. GIVOGRI, K.-Y. TSENG, S. ALFORD, E. R. BONGARZONE;
Univ. of Illinois at Chicago, Chicago, IL

Abstract: Lysosomal storage diseases (LSDs) are characterized by decreased activity of lysosomal enzymes leading to the accumulation of undegraded material. Many LSDs course with cognitive, learning limitations and neuronal dysfunction. Amongst LSDs, Krabbe disease (KD) is a fatal LSD caused by mutations of Galactosylceramidase (GALC), triggering the accumulation of the sphingolipid psychosine, with subsequent demyelination and neurodegeneration of central and peripheral nervous system. Three classes of KD are known (infantile, juvenile or adult), being the infantile form the most frequent and severe. Importantly, the effects of GALC deficiency observed in the infantile form of KD can be recapitulated in the Twitcher (Twi), a KD mouse model that exhibits null GALC activity and consequently psychosine accumulation. Although demyelination is deemed as the primary cause of neuropathology in KD, recent findings have shown that neuron-restricted GALC deletion is sufficient to induce motor, neuro-axonal, and behavioral impairments. Thus, the mechanism of neuronal disease in KD is not clear, but we hypothesize that psychosine accumulation exerts detrimental effects directly in neuronal function and structure. To test this idea, we analyzed synaptic function by employing electrophysiological recordings of hippocampal slides from TWI mice, mice with GALC deletion restricted to oligodendrocytes (PLP-CreERT2/Flx-GALC-Flx) or neurons (CamKII-CreERT2/Flx-GALC-Flx). In turn, synaptic structure was evaluated by ultrastructural, immunohistochemical and biochemical analyses in wild-type (WT) or TWI mice brains. Also, the potential mechanisms of psychosine effects were analyzed by *in vitro* synaptic vesicle fusion measurements along with behavioral memory tests. Our results shown that ubiquitous GALC mutations lead to decreased Paired-Pulse Facilitation (PPF) of CA1 neurons in TWI compared to WT. Interestingly, decreased PPF was only observed upon GALC ablation in neurons but no in oligodendrocytes. Furthermore, we observed structural disruptions in pre- and postsynaptic domains of TWI brains, including decreased number of synaptic vesicles (SV) and dendritic spines. Psychosine reduced the fusion of SV and accumulated ~150-fold in the synaptosome of TWI at final stages of the disease. Finally, WT mice subjected to psychosine administration exhibited impaired memory performance. Altogether, our findings reveal a pathogenic mechanism where the local accumulation of undegraded psychosine at the synapse is sufficient to interfere with synaptic function in the TWI hippocampus by reducing SV fusion and altering synaptic structure.

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Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.13/Q3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: the National Key Research and Development Program of China (2021YFA1101802 and 2019YFA0802703)
the National Natural Science Foundation of China Grants (82022021, 81971189, 81922022, and 91849117)
the Jiangsu Province Innovative and Entrepreneurial Team (2018).

Title: Molecular mechanism of HSF1 mislocalization and SWI/SNF complexes in Huntington's disease

Authors: *C. LIU, X. GUO;
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Abstract: Molecular mechanism of HSF1 mislocalization and SWI/SNF complexes in Huntington's disease**Chunyue Liu**, Xing Guo*
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Abstract: Huntington's disease(HD) is an autosomal dominant genetic disease caused by the huntingtin(htt) gene on chromosome 4. There is currently no effective treatment. Therefore, it is significant to study the molecular mechanism of HD. We found abnormal mitochondrial localization of heat shock transcription factor 1 (HSF1) in HD. Results showed that mislocalized HSF1 activates the phosphorylation of mitochondrial dynamin-related protein 1 (Drp1) S616 site and inhibits the oligomers formation of mitochondrial single-strand DNA-binding protein 1 (SSBP1), which in turn leads to mitochondrial dysfunction and neurodegeneration. The peptide DH1 which can reduce mitochondrial translocation of HSF1 can improve mitochondrial dysfunction and delay disease progression in HD.Based on the single-cell RNA sequencing and immunofluorescence experiment in previous studies, we found that the proportion of medium spiny neurons decreased in D60 HD striatal organoids which correlated with the fetal striatum at 12 to 19 weeks post-conception, and transcription of multiple genes is severely disrupted, while gene expression is regulated by chromatin remodeling complexes. In this study, we found that the expression of some subunits of the SWI/SNF chromatin remodeling complex of in HD mice YAC128/CAG140 was abnormal. Most subunits such as BAF170/SMARCA4/BAF60a were decreased at YAC128. Interestingly, BRD7 was increased and the other subunits were

unchanged. Furthermore, we found that BCL7B was less at CAG140. These results mean that the function of the SWI/SNF complex is impaired in HD mouse models. Meanwhile we also obtained consistent conclusions in HD iPSC and D30 cortical organoids. We supposed that HD may be caused by chromatin remodeling complexes changes leading to epigenetic abnormalities which contribute to the development of HD.
Keywords: Huntington's disease, heat shock factor 1(HSF1), SWI/SNF complex

Disclosures: **C. liu:** None. **X. guo:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.14/Q4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: New Jersey TBI grant

Title: Phosphodiesterase 1 signaling dysfunction associated with cognitive deficits in Alzheimer’s disease

Authors: Y. YAN[1], ***Y. XU**[2];
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Abstract: Phosphodiesterase 1 signaling dysfunction associated with cognitive deficits in Alzheimer’s disease
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Background: Alzheimer’s disease (AD) is a neurodegenerative disorder associated with irreversible cognitive impairment and memory loss. Phosphodiesterases (PDEs) consisted of 11 subtypes (PDE1 to PDE11) and over 40 isoforms that regulate levels of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). Among them, PDE1 has been demonstrated to be a potential drug target for a variety of diseases ranging from cardiovascular disease and neurodegenerative disorders including AD.
Method: This study used public gene expression data from Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) to decipher the role of PDEs, particularly PDE subtype 1A dysfunction in pathology of Alzheimer’s disease by analyzing the mRNA and lncRNA differences in the GENECODE data resource V22 (https://www.gencodegenes.org/). The mRNA and lncRNA were extracted from the RNA-seq cohort with five eligible Alzheimer Disease (AD) cohorts included. Human Embryonic Kidney 293 cells were chosen for PDE1A ceRNA validation using dual-luciferase Assay.
Result: 12584 differentially expressed genes (DEGs) were identified when compared the difference between AD brain and age-matched control groups. Among them, there were 1459

mitochondrial related DEGs were found, while 1131 AD-related mitochondrial genes were significantly changes in AD brain by Venn plot analysis. The subsequent study found that among two clusters, mitochondrial genes regulated the pathogenesis of AD with interaction of PDE1A through
mitochondrial-related ceRNA network. Generation of AD-related mitochondrial signature (ARMS) by machine learning method found downstream immunity genes were to AD, may be activated by regulation of PDE1A dependent cellular immunity.
Conclusion: These findings implicate that PDE1A activity may affect cellular immunity by AD patients during regulation of mitochondrial metabolic process.
Key words: PDEs, PDE1A, ceRNA, mitochondrial function, cellular immunity, Alzheimer's disease

Disclosures: Y. Yan: None. **Y. Xu:** None.

Poster

PSTR262. Neurodegenerative Disease: Mitochondrial and Lysosomal Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.15/Q5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Wellcome Trust Grant 210904/Z/18/Z/WT

Title: Functional identification of the promoter regions of human NMNAT2 and SARM1 and investigation of human variants in these regions on gene expression

Authors: *E. R. WILSON[1], H. MORSY[2], L. CARLTON[1], J. GILLEY[1], H. HOULDEN[2], M. M. REILLY[2], M. P. COLEMAN[1];
[1]Dept. of Clin. Neurosciences, Univ. of Cambridge, Cambridge, United Kingdom; [2]Dept. of Neuromuscular Disorders, Univ. Col. London, London, United Kingdom

Abstract: The programmed axon degeneration pathway (or Wallerian degeneration) has become an important drug target in a bid to tackle neurodegenerative diseases. Protein coding mutations in two of the key genes involved in this pathway, *NMNAT2* and *SARM1*, are associated with human neurodegenerative diseases including ALS and peripheral neuropathy (Huppke et al., 2019, Lukacs et al., 2019, Gilley et al., 2021, Bloom et al., 2022, Dingwall et al., 2022). Links to this pathway have also been proposed in other human diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, glaucoma and traumatic brain injury. SARM1, an NAD+ degrading enzyme, is considered the central executioner of programmed axon degeneration. In the uninjured axon, SARM1 activity is repressed by NMNAT2, an NAD+ synthesising enzyme. Mouse studies have highlighted that the relative levels of *NMNAT2* and *SARM1* could impact disease progression and neurodegenerative outcome (Gilley et al., 2013, Gilley et al., 2019, Gould et al., 2021). Thus, understanding how human *NMNAT2* and *SARM1* are regulated on a transcriptional level has the potential to identify critical regions of these genes in which variation

may modulate patient outcomes and disease progression. In the present study we use *in vitro* models and luciferase assays to identify the promoter regions of human *NMNAT2* and *SARM1* which are essential for their expression. Moreover, preliminary data indicates a non-coding region 5' of the canonical transcription start site of human *NMNAT2* that represses expression, specifically in neuronal cells. Finally, we identify human variants in the promoter regions of *NMNAT2* and *SARM1*, including a homozygous variant in peripheral neuropathy, and explore the impact of said variations on expression levels. In sum, this work describes the promoter regions important for human *NMNAT2* and *SARM1* expression, and begins to investigate how changes in expression levels of these genes may contribute to human disease. Advances in whole genome and exome sequencing studies and genomic databases are likely to expand our understanding of the role of the programmed axon degeneration pathway and in which human diseases it is most relevant.

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Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.01/Q6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MCIN/AEI/10.13039/501100011033, grant PID2019-106285RB
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H2020 874583
FIS/FEDER 19/1338
FIS/FEDER 16/1288
AICO/2020/285
CIAICO/2021/132
MS20/0006
MS21/0133

Title: High levels of anti-inflammatory epoxyeicosatrienoic acids may improve neurodevelopment in children prenatally exposed to mercury

Authors: *C. SANFELIU[1], C. BARTRA[1], S. LLOP[2,3], J. KULIGOWSKI[4], A. ALBIACH-DELGADO[4], C. SUÑOL[1], E. RODRÍGUEZ-FARRÉ[1], F. BALLESTER[2,3,5], R. SOLER-

BLASCO[2,3,5], B. JORA[6], J. JARNE-FERRER[6], C. GRIÑÁN-FERRÉ[6,7], S. VÁZQUEZ[6], M. PALLÀS[6,7];
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Abstract: A balanced concentration of polyunsaturated fatty acids (PUFA) in the prenatal stage is essential for children's neurodevelopment. Also, animal studies showed that high levels of anti-inflammatory PUFA metabolites in the embryonic brain protect against genetic or environmental insults that would otherwise cause cognitive impairment. Here we used liquid chromatography - mass spectrometry to analyze oxylipins, the oxygenated metabolites of PUFA, in the placenta tissue (N=12) and cord blood plasma (N=39) of children from the INMA cohort (Valencia, Spain). Both tissues were characterized for total Hg levels as a reference for developmental neurotoxic MeHg exposure during pregnancy and distributed in low and high Hg groups. Deleterious effects of high Hg were confirmed in the placenta as decreased proteasome activity and inhibitory epigenetic changes. Children's neurodevelopment was assessed using the Bayley (14 months) and McCarthy (5 years) scales. Spearman correlation coefficients were calculated between scores and oxylipin levels. We also analyzed cortical brain tissue from wild type and transgenic Alzheimer's disease (5XFAD) mice dosed for 2 months with vehicle or a soluble epoxide hydrolase enzyme (sEH) inhibitor, UB-BJ-02 (5 mg/Kg, N=5/group). Inhibition of sEH increases levels of the potent anti-inflammatory epoxyeicosatrienoic acids (EETs) by inhibiting their hydrolysis to dihydro-EETs (DiHETs). We found that DiHETs were increased in the placenta of high Hg group. Furthermore, the mental and psychomotor development of 14-month-old children correlates positively with DiHETs levels in both placenta and cord blood tissues. Interestingly, cord blood DiEHTs positively correlate with working memory at 5 years. Thus we suggest that higher levels of DiHETs indicate higher synthesis of their anti-inflammatory EETs precursors. Accordingly, placenta levels of EETs correlate with mental development at 14 months of age. Other oxylipin changes also suggested an involvement of inflammatory mechanisms in the neurodevelopment of children exposed to MeHg. In general, higher levels of markers of resolved inflammation or final stable metabolites in the placenta and cord blood tissues correlate with better neuropsychological development in children exposed to environmental MeHg. Finally, mouse treatment with the drug UB-BJ-02 showed increased EETs and decreased pro-inflammatory markers in brain tissue. Both human and experimental results showed that EETs are prominent anti-inflammatory metabolites and support sEH inhibition as an anti-inflammatory treatment to increase brain resilience to environmental risk of neurodevelopmental damage.

Disclosures: **C. Sanfeliu:** None. **C. Bartra:** None. **S. Llop:** None. **J. Kuligowski:** None. **A. Albiach-Delgado:** None. **C. Suñol:** None. **E. Rodríguez-Farré:** None. **F. Ballester:** None. **R. Soler-Blasco:** None. **B. Jora:** None. **J. Jarne-Ferrer:** None. **C. Griñán-Ferré:** Other; Inventor of the Universitat de Barcelona patent application on sEH inhibitors WO2022200105. **S. Vázquez:** Other; Inventor of the Universitat de Barcelona patent application on sEH inhibitors WO2022200105. **M. Pallàs:** Other; Inventor of the Universitat de Barcelona patent application on sEH inhibitors WO2022200105.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.02/Q7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CIHR Grant No. PJT-162144
St. Boniface Hospital Research Foundation Grant Nos. 1406–3216 and 1410–3216
University of Manitoba

Title: 17 beta estradiol enhances neurite outgrowth by activating ampk, pgc1a and atf3 in adult dorsal root ganglion neurons

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Abstract: Rationale: Dorsal root ganglion (DRG) sensory neurons express both estrogen receptors (ERs) alpha and beta in male and female rodents. 17-beta estradiol which is the most potent form of estrogen plays a crucial role in the development and survival of adult DRG neurons, as well as the regulation of neurite outgrowth. Additionally, AMP-activated protein kinase (AMPK) serves as a cellular energy sensor and can modulate the levels of activating transcription factor 3 (ATF3) and PGC-1α. These target proteins are involved in neuronal regeneration and mitochondrial biogenesis. In our study, we hypothesized that activation of ERs with 17-beta estradiol could enhance the energy metabolism in adult DRG neurons and also promote their axonal sprouting. **Objective:** Investigate the impact of 17-beta estradiol treatment and gain a comprehensive understanding of the ER signaling pathway in adult rat DRG neurons. **Methods:** DRG neurons derived from adult male or female Sprague Dawley rats were isolated and cultured under defined conditions for 24 hours. Subsequently, the cultured neurons were treated with 17-beta estradiol. The expression levels of pAMPK, ATF3, and PGC-1α were determined using western blotting. Furthermore, mitochondrial parameters, including basal respiration and ATP production, were assessed using the Seahorse XF24. Immunostaining for ER alpha and ER beta was also conducted. Additionally, DRG neurons were stained with β-tubulin III and captured images were subsequently analyzed using ImageJ to evaluate total neurite outgrowth. We also blocked AMPK using Compound C to investigate its effects on ATF3 and axonal sprouting. **Results:** Immunocytochemical analysis confirmed the presence of both ER alpha and ER beta in adult DRGs. Treatment with 17-beta estradiol resulted in a dose-dependent increase in phosphorylated AMPK (pAMPK) levels in male and female DRG neurons. Furthermore, protein levels of ATF3 and PGC-1α were also elevated in response to estradiol treatment. Additionally, estradiol treatment enhanced basal respiration in these cells and, DRG neurons derived from both male and female rats exhibited increased neurite outgrowth

upon estradiol treatment. Notably, inhibition of AMPK with Compound C also inhibited estradiol mediated ATF3 activation. **Conclusion:** Our findings suggest that 17-beta estradiol stimulates neuronal outgrowth in adult rat DRGs through the activation of pAMPK, PGC-1α, and ATF3, with AMPK acting upstream of ATF3. These results suggest that 17-beta estradiol may have therapeutic implications for treating neurodegenerative conditions, including peripheral neuropathy.

Disclosures: **P. Mishra:** None. **P. Fernyhough:** None. **B. Albensi:** None.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.03/Q8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DoD-VRP-W81XWH2010694

Title: Prophylactic Treatment with the Secretome of Cultured Amnion-Derived Multipotent Progenitor Cells Reduces the Consequence of Traumatic Optic Neuropathy

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Abstract: Background: The proposed project investigates a prophylactic treatment of ST266 delivered intranasally to prevent cell death in the visual system of military personnel who are at high risk to experience traumatic head/eye injuries during training activities or deployment. ST266 is a proprietary secretome obtained by culturing a novel population of cells termed Amnion-derived Multipotent Progenitor cells under proprietary, pharmaceutical grade GMP conditions. ST266 contains hundreds of biologically active proteins and other factors that have been shown to be neuroprotective and anti-inflammatory; it promotes cell recovery and tissue healing. We used our preclinical mouse model of mild injury (mTBI), in which we have demonstrated TBI-dependent visual dysfunction. Here we report the results of a prophylactic treatment with a single intranasal dose of ST266 24 h prior to the first injury. **Method:** We tested a known therapeutic dose of volume of 10µL via intranasal delivery 24 h prior to the first injury and at 8 am on the day of the injury (with an impact scheduled at noon) and treated every morning for the next 9 days until the beginning of the behavioral tests in male C57BL/6 mice using our mouse model of traumatic optic neuropathy (TON). Learning, memory, and visual deficits were assessed with the Barnes Maze and optomotor behavioral tests starting 10 days post first-injury. **Results:** ST266 improved learning but not spatial memory within the Barnes Maze

starting at 10 days post injury. The optomotor response frequency significantly decreased with increasing Cycles Per Degree in response to injuries, but no treatment effect was observed. ST266 treatment significantly reduced the loss of retinal ganglion cells (RGC) as quantified by Brn3a immunolabeling at 10 days post injury compared to PBS-treated mice. ST266 treatment also attenuated astrogliosis, microgliosis, and leukocyte infiltration in the optic nerve of the injured mice. Sections immunostained with $Olig2^{+}$ showed a proliferation of oligodendrocytes at 10 days post last injury which was reduced after ST266 treatment. Biochemical analysis of the optic nerve revealed activation of the NLRP3 inflammasome in our model of TON that was alleviated after a prophylactic treatment with ST266. **Conclusion:** This study found that r-mTBI lead to TON and that increased inflammation in the optic nerves, acute neurobehavioral dysfunctions, and loss of retinal ganglion cells were mitigated by a prophylactic treatment with ST266.

Disclosures: B. Mouzon: None. **M. Browning:** None. **N. Carothers:** None. **M. Koprivica:** None. **S. Ferguson:** None. **L. Brown:** A. Employment/Salary (full or part-time):; noveome Biotherapeutics, Inc.. **R. Mccartan:** None. **H. Wessel:** A. Employment/Salary (full or part-time):; Noveome Biotherapeutics Inc.. **R. Tzekov:** None. **F. Crawford:** None.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.04/R1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Hong Kong Research Council General Research Fund (GRF 15104019)

Title: Maternal Exercise Improves Hippocampal Synaptic Plasticity And Depressive-like Behavior In Adult Offspring

Authors: *S. YAU, J. MADEDO;
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Abstract: Maternal physical exercise during pregnancy has been reported to benefit offspring's brain health. We have previously shown that maternal exercise promotes adult hippocampal neurogenesis and reduces depressive behaviours. However, the underlying mechanisms of these transgenerational effects are largely unknown. We aim to further examine whether maternal exercise improves hippocampal neuroplasticity to reduce depression-like behavior in offspring. Pregnant female mice with C57BL/J background were allowed to access to running wheels in the housing cages throughout the gestational period. Male and female mice offspring at the age of 6 weeks were sacrificed for either electrophysiology or Western blot analysis. Our results showed that maternal exercise showed main effects in increasing hippocampal protein levels of PSD-95 and BDNF, and synaptophysin in offspring. These molecular changes were associated with a significant increase in long-term potentiation in the perforant path projections to the hippocampal

dentate region of both male and female offspring. To test whether maternal exercise increases stress resilience of offspring, we subjected the offspring to 21-day unpredictable chronic stress. Results showed that maternal exercise attenuated the increase in immobility time in forced swim test and reduction in grooming time reduced by 21-day chronic unpredictable stress in both male and female offspring. These findings have suggested that maternal exercise could improves hippocampal function and protect offspring against stress-induced hippocampal synaptic impairment.

Disclosures: S. Yau: None. **J. Madedo:** None.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.05/R2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONAHCYT Grant 285184
CONAHCYT Postdoctoral Fellowship I1200/224/2021
DGAPA-PAPIIT, UNAM (216422)

Title: The neuroprotective effect of epoxyeicosatrienoic acids (EETs) during apoptotic neuronal death is partially mediated by ROS reduction

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Abstract: Cytochrome P450 (CYP) epoxygenases and their metabolic products, epoxyeicosatrienoic acids (EETs), have been proposed as therapeutic targets in the brain due to its diverse and beneficial properties. In particular, EETs have been reported to have a protective effect against neuronal apoptosis and oxidative stress conditions. However, it has not been established a relationship between the EETs-mediated neuroprotection and its possible regulation of reactive oxygen species (ROS). Therefore, we studied the role of ROS in the EETs-mediated neuroprotection in a model of neuronal death. For this purpose, we used primary cultures of cerebellar granule neurons. We induced cell death with staurosporine (0.5 micromolar), glutamate (300 micromolar) or potassium deprivation (5 mM KCl, K5) treatments for 24 h. To enrich the content of EETs in neuronal cultures, cells were pre-treated for 2 h with TPPU (10 and 100 micromolar), a specific soluble epoxide hydrolase (sEH) inhibitor. Cell viability was assessed by calcein/propidium iodide staining and ROS levels were measured with dihydroethidine (DHE). Under these conditions, we found that TPPU pre-treatment induced a marked neuroprotective effect in staurosporine-induced death by significantly increasing cell viability and significantly decreasing ROS production in a TPPU dose-dependent manner. On the other hand, when cells were treated with glutamate or K5, cell viability was only recovered by 10

micromolar TPPU treatment. In both cases, we observed a reduction of ROS production. These results suggest that ROS reduction may be involved in the EET-mediated neuroprotection.

Disclosures: C. Navarro-Mabarak: None. **G. Domínguez:** None. **J. Moran:** None.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.06/R3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The longevity treatment, 17α-estradiol, improves metabolic and peripheral nerve parameters in middle aged and older male mice

Authors: *M. BLASZKIEWICZ[1], J. WILLOWS[1], W. ARNOLD[2], P. REIFSNYDER[3], D. HARRISON[3], K. TOWNSEND[1];
[1]The Ohio State Univ. Col. of Med., Columbus, OH; [2]Univ. of Missouri, Univ. of Missouri, Columbia, Columbia, MO; [3]The Jackson Lab., Bar Harbor, ME

Abstract: 17α-Estradiol longevity treatment improves metabolic and peripheral nerve parameters in middle aged and older male mice

Magdalena Blaszkiewicz[1], Jake Willows[1], William David Arnold[1], Peter Reifsnyder[2], David Harrison[2], Kristy L. Townsend[1]
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Sex differences underlie the onset and severity of numerous diseases, and biological sex likely interacts with genetics in the presentation of disease phenotypes. Age-related peripheral neuropathy (PN) is a top cause of small fiber neuropathy in humans, and we previously demonstrated that PN impacts subcutaneous adipose tissue of aged mice and humans as well. We and others have reported less severe diabetic PN in mice, and we have found protection from age-related PN until the age of reproductive senescence in female mice, but PN was not mitigated with rapamycin longevity treatment in aged HET3 mice of either sex. In fact, rapamycin exacerbated age-related dysregulation of adipose tissue. The genetically diverse HET3 mice are utilized by the NIA's intervention testing program (ITP) to identify longevity treatments, so given the likelihood that sex hormones play a role in PN, we tested another validated ITP longevity treatment,17α-Estradiol (17α-E2) for effects on adipose and PN across aging. This treatment is non-feminizing and previously proven to extend lifespan in male HET3 mice. Middle aged (~51 wks) and older (~84 wks) male HET3 mice received 17α-E2 treatment in the diet for 17 weeks. We observed increased grip and contractility torque and improved NMJ function in middle aged 17α-E2 treated mice. However, 17α-E2 treatment improved intraepidermal innervation (a histological measure of small fiber PN) in the older mice only. Reduced fat mass was seen in all 17α-E2-treated mice regardless of age, with improved glucose sensitivity evident only in the older male mice. Increased energy expenditure was seen in 17α-E2

treated middle aged mice. Interestingly, these metabolic and neural endpoint data also varied by genetic strain contribution. For example, grip strength improvement was most evident when C57BL/6 or DBA/2 strain contribution was low in the HET3 mice. Studies in female HET3 mice given 17α-E2 across aging are underway, but taken together, we found that 17α-E2 treatment is a translationally relevant way to maintain metabolic and nerve health across aging.

Disclosures: **M. Blaszkiewicz:** None. **J. Willows:** None. **W. Arnold:** None. **P. Reifsnyder:** None. **D. Harrison:** None. **K. Townsend:** None.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.07/R4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Restore visual function in mice with glaucoma by optogenetic enhancement of mitochondrial function

Authors: *Y. WANG[1], B. YAN[2], J. ZHANG[2];
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Abstract: Objective and rationale Glaucoma is the leading cause of irreversible blindness worldwide. People with glaucoma suffer from terrible visual deficits caused by progressive degeneration of retinal ganglion cells (RGCs). As predicted, over 100 millions people will be affected by glaucoma, however, there are no radical therapies up to now. There is an urgent need for developing effective therapies. Previous studies showed that mitochondrial abnormalities, both anatomical and functional, are highly associated with glaucoma. Here we explored whether optogenetic enhancement of mitochondrial function could restore visual function induced by glaucoma. **Methods and results** Here we used mtGAPR mice, one transgenic mice carrying opsins in mitochondria across body, along with a silicone-oil induced ocular hypertension model to imitate angle-closure glaucoma on mice. During the experiment, green light was given 4h per day to optogenetically enhance mitochondrial function within mice. To assess whether glaucoma was induced, intraocular pressure (IOP) of experimental mice was monitored weekly. Mice with relatively high IOP after injection were included in the experiment. RGCs counting showed that more percentage of RGCs survived in optogenetically enhanced transgenic mice compared to wildtype mice after injection, especially in the first two weeks. Together with visual acuity test, indicated by optomotor response, confirmed that glaucomatous visual deficits were partially rescued by optogenetic enhancement of mitochondrial function. Optogenetic activation of mitochondria could also delay the glaucomatous progress in mitochondria-linked AAV-intravitreally-injected mice. To further explore the protection mechanisms, we found that the protective effect might be associated with the interference of pyroptosis. **Conclusions** Our work showed that rescuing mitochondrial dysfunction could partially protect RGCs from degeneration in glaucoma.

Disclosures: **Y. Wang:** None. **B. Yan:** None. **J. Zhang:** None.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.08/R5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Netrin-1 and neurodegenerative diseases: Unraveling Therapeutic Avenues

Authors: *I. PEDIADITAKIS[1], J. MCCARTHY[2], A. J. MASON[1], R. JONES[2], B. HOLUB[1], J. OSBOURN[2], M. M. SIDOR[1];
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Abstract: Netrin-1, a key player in embryonic axonal guidance, has been recognized as a significant factor in synaptic plasticity, neuroprotection, and inflammation regulation within the mature brain. Recent studies have reported altered Netrin-1 levels in neurodegenerative diseases such as Parkinson's Disease (PD) and Alzheimer's disease (AD), suggesting its potential role in disease pathogenesis. We explored Netrin-1's role in neurodegeneration via immunodepletion of Netrin-1 in iPSC-derived motor and dopaminergic neurons cultures, αSyn fibrils induced iPSC models of PD, and TDP43 iMotor neuron models of ALS (Q331K variant). Our data indicate that Netrin-1 depletion induces loss of synaptic proteins and cell death. Further experiments using two-compartmental microfluidic devices revealed axonal reduction caused by Netrin-1 deprivation. Treatment with recombinant Netrin-1 rescued some of these effects, elevating synaptic proteins and suggesting its potential to foster synaptic function and formation. We also noticed a significant impact of Netrin-1 treatment on neurons' functional connectivity and firing behavior, as indicated by changes in the mean firing rate and network burst frequency. In summary, Netrin-1 has demonstrated the potential to reverse key pathological features associated with PD and ALS, such as cell death and synaptic dysfunction. These findings pave the way for further exploration of the roles of Netrin-1 and its receptors in neurodegeneration, highlighting the promise of this pathway for future therapies.

Disclosures: **I. Pediaditakis:** A. Employment/Salary (full or part-time):; Full-time, Alchemab Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options, Alchemab Therapeutics. **J. McCarthy:** A. Employment/Salary (full or part-time):; Full Time, Alchemab Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alchemab Therapeutics. **A.J. Mason:** A. Employment/Salary (full or part-time):; Alchemab Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alchemab Therapeutics. **R. Jones:** A. Employment/Salary (full or part-time):; Full time, Alchemab Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alchemab

Therapeutics. **B. Holub:** A. Employment/Salary (full or part-time):; Full time, Alchemab Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alchemab Therapeutics. **J. Osbourn:** A. Employment/Salary (full or part-time):; Full time, Alchemab Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alchemab Therapeutics. **M.M. Sidor:** A. Employment/Salary (full or part-time):; Full Time, Alchemab Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Alchemab Therapeutics.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.09/R6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NSTC Grant 111-2320-B-906 -001 -MY3

Title: Exploring the Efficacy of Paeonol in Alleviating Chemotherapy-Induced Peripheral Neuropathy (CIPN): A Basic Research Study

Authors: *C.-C. HUANG[1,2], Y.-H. CHEN[3];
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) causes disabling pain involving damage to the peripheral motor, sensory and autonomic neurons. Paeonol, the major component of Moutan Cortex, has neuroprotective effects by improving neuronal morphology, increasing neuronal activity, inhibiting microglia activating, reducing oxidative stress, and exhibiting anti-inflammatory effects. The mechanisms involved in CIPN include neuroinflammation and altered excitability of peripheral neurons. Adiponectin, a hormone primarily secreted by adipose tissue, plays a crucial role in the intricate interactions of the central and peripheral nervous systems. Through activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPARα) signal pathway, adiponectin has been shown to regulate neurotransmitter release and modulate neuronal excitability, ultimately influencing cognitive functions, mood regulation, and neuroinflammation. To date, no trial has investigated the efficacy of paeonol in treating chemotherapy-induced peripheral neuropathy in cancer patients Intraperitoneal administration of paclitaxel (5 mg/kg i.p. on days 0 and 2) reduced the mechanical and thermal pain threshold in the hind paw, indicating an increased mechanical and thermal allodynia. Conversely, oral administration of paeonol at doses of 100 mg/kg and 200 mg/kg significantly reversed the decrease in mechanical pain threshold induced by paclitaxel on day 6, day 10, day 13, and day 15 in the mechanical pain test. In the thermal pain test, oral administration of paeonol at a dose of 200 mg/kg also reversed the decrease in thermal pain

threshold induced by paclitaxel on the same days. It indicates that paeonol improved in the mechanical and thermal allodynia. An RNA sequencing study was conducted to identify the genes affected by paclitaxel and paeonol in the dorsal root ganglion. The results revealed that genes related to adiponectin pathways were upregulated by paeonol. Western blot results demonstrated that paclitaxel increased the expression of adiponectin in both the spinal cord and serum, and these effects were further enhanced by paeonol. These findings suggest that paeonol may protect against the paclitaxel-induced peripheral neuropathy by increasing the expression of adiponectin in serum and nervous tissue. Our data are expected to provide evidence for the neuroprotective effects of paeonol on CIPN and contribute to the development of new approaches for its treatment.

Disclosures: C. Huang: None. **Y. Chen:** None.

Poster

PSTR263. Neuroprotective Mechanisms: Endogenous Molecules and Other Approaches

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.10/R7

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Joint research with Ushio, Inc.

Title: Morphological analysis and deep learning prediction for peripheral neurotoxicity using cultured neurons in microfluidics

Authors: *I. SUZUKI, X. HAN, N. MATSUDA;
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a major common adverse event associated with neurological abnormalities. An accurate assessment is essential to improve knowledge about CIPN incidence, and cultured neurons (i.e., primary rodent dorsal root ganglia (DRG), human iPS derived sensory) have recently been developed as *in vitro* models to study CIPN at the mechanistic level. In the present study, we developed a microfluidic device for structured culture of DRG and human iPS derived sensory neurons, and predict neurotoxicity induced by anticancer drugs based on neurites morphological analysis. This microfluidic culture device could separate the cell body and neurites, so that elongated neurites morphology can be analyzed alone. COP (Cyclo olefin polymer), which has excellent observability and low drug adsorption, is used as the resin material, and the bottom surface is created thin and flat enough for a clear view by microscope. Next, DRG or iPS sensory neurons was cultured in the device coated with Poly-L-lysine and Laminin. After culturing with a specific medium containing insulin, neurites grew sufficiently to occupy almost the whole microfluidic channel area, and the axon elongated unidirectional along the horizontal direction. The morphological changes of neurites can be clearly analyzed by immunostaining. After administration of several typical anti-cancer drugs, the morphological characteristics were analyzed by calculating neurite-related

parameters, especially neurite aggregation and induced hollowing. In addition, peripheral neurotoxicity was predicted by a deep learning AI trained with neurites image datasets. After training, AI could accurately detected neurotoxicity even at low concentrations. Therefore, this microfluidic device combined with morphological analysis is an effective *in vitro* toxicity assessment platform for peripheral neuropathies.

Disclosures: I. Suzuki: None. **X. Han:** None. **N. Matsuda:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.01/R8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Long-term intraocular pressure fluctuation & epiretinal membrane in patients with glaucoma or glaucoma suspect

Authors: *K. JUNG[1], C. PARK[2];
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Abstract: Epiretinal membrane (ERM) is a phenotype of a reactive gliosis because formation of ERM involves glial proliferation in response to retinal injury or disease involving inflammatory and glial cells. Glaucoma is characterized by progressive degeneration of retinal ganglion cells, for which increased intraocular pressure (IOP) is the most important risk factor. The associations between ERM and glaucoma were suggested in several studies. In an animal model undergoing intermittent IOP elevations, a reactive gliosis, a phenotype of ERM, was found in the optic nerve head. We investigated the association between IOP fluctuation and idiopathic ERM in patients with glaucoma or glaucoma suspect. In this retrospective study, a total of 84 patients with glaucoma or glaucoma suspect were included. Among them, forty one patients had no ERM and forty three patients had ERM. Long-term fluctuation of IOP was defined as the standard deviation (SD) of IOP at all visits. Patients were divided into two groups according to the median value of SD of IOP: the low IOP fluctuation group and high IOP fluctuation group. Among patients with available heart rate variability (HRV) data, the relationship between the HRV parameter and IOP fluctuation was analyzed. Patients with ERM was older and had higher IOP fluctuation and higher proportion of having history of cataract surgery and greater macular thickness (P=0.018, 0.049, 0.013, <0.001). The high IOP fluctuation group showed higher proportion of patients with ERM (62.5%) than the low IOP fluctuation group (36.4%, P=0.028). In the multiple logistic analysis, higher IOP fluctuation group were associated with the presence of ERM (P=0.047). Among patients with ERM, eyes with stage 3 or 4 ERM had worse visual field defects based on mean deviation than those with stage 1 or 2 ERM (P=0.025). The high IOP fluctuation group showed higher level of low frequency HRV, an index of sympathetic cardiac

control than the low IOP fluctuation group (P=0.027). Intereye comparison in eyes with ERM and the fellow eyes without ERM, eyes with ERM (2.2±0.9 mmHg) had higher fluctuation of IOP than those without ERM (2.0±0.8 mmHg, P=0.029). In conclusion, long-term IOP fluctuation had the relevance to idiopathic ERM in patients with glaucoma or glaucoma suspect. In glaucoma patients with ERM, more advanced stage ERMs were associated with worse visual field damage. Further studies are needed to determine if long-term IOP fluctuation affects the progression of glaucoma and reactive gliosis.

Disclosures: K. Jung: None. **C. Park:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.02/S1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DGAPA-PAPIIT-UNAM 213123 to F.B.R.
Departamento de Ciencias de la Salud

Title: Persistent Impairment of Spatial Memory and Hippocampus Neuronal Plasticity long after Repeated Intraperitoneal Injections of Lipopolysaccharide.

Authors: *E. GUTIERREZ-LOPEZ[1], K. R. GUZMAN-RAMOS[2], D. OSORIO-GÓMEZ[3], F. BERMÚDEZ-RATTONI[4];
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Abstract: Neuroinflammation has been implicated in cognitive impairments associated with various neurological disorders related to memory. In this study, we aimed to investigate the effects of repeated lipopolysaccharide (LPS) intraperitoneal injections on spatial memory and neuronal plasticity in the hippocampus. Adult Wistar male rats were subjected to either saline or 5 LPS injections (250 μg/kg or 500 μg/kg) every 72 hours. LPS effects, Memory test, and neuronal plasticity were evaluated 1 week and 8 weeks after injections in independent groups. LPS effects in animals were measured by weight, spatial memory was assessed using the Morris Water Maze test (MWM), and neuronal plasticity was evaluated by Long Term Potentiation (LTP) on Perforant Pathway - Dentate Gyrus in the hippocampus. Our results revealed that rats receiving repeated LPS injections (250 μg/kg and 500 μg/kg) exhibited a significant weight lost during the treatment, but they regain weight one week after the last injection and this persisted 8 weeks later. Rats that received LPS injections (250 μg/kg and 500 μg/kg) showed impairment in spatial memory 1 week after treatment compared to the saline-treated group ($p < 0.05$). Additionally, LPS 250 μg/kg-treated group caused a lower LTP than the control group, and LPS 500 μg/kg-treated group induced but did not maintain the LTP ($p < 0.01$). Furthermore, we

assessed the long-term effects of LPS injections. Remarkably, the spatial memory impairment persisted only in the LPS 500 μg/kg-treated group even at this time point ($p < 0.05$). Neuronal plasticity alterations continued similarly in the LPS 500 μg/kg-treated group ($p < 0.05$), but the LPS 250 μg/kg-treated group increased the LTP at the same level that the saline-treated group ($p < 0.01$). In conclusion, repeated intraperitoneal injections of LPS induce persistent spatial memory deficits and alterations in neuronal plasticity in the hippocampus. The persisting impairments observed even eight weeks after treatment suggest long-lasting consequences of neuroinflammation. Further investigations are warranted to elucidate the underlying mechanisms and potential therapeutic interventions to mitigate these detrimental effects.

Disclosures: E. Gutierrez-Lopez: None. **K.R. Guzman-Ramos:** None. **D. Osorio-Gómez:** None. **F. Bermúdez-Rattoni:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.03/S2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: New York State Department of Health C33267GG
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (Program)
NIH Blueprint for Neuroscience Research MH119346
NIH Blueprint for Neuroscience Research T32 NS07222

Title: Sarm1 deficiency regulates neuron intrinsic and extrinsic mechanisms of axon regeneration in the injured mammalian PNS

Authors: *H. J. HAFNER[1], L. B. SCHMITD[1], M. ATHAIYA[1,2], E. ASGHARI-ADIB[3], R. KOHEN[1,2], A. L. KALINSKI[1,4], R. J. GIGER[1,2];
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Abstract: Injury to the mammalian peripheral nervous system triggers programmed disintegration of distal nerve fibers, a process known as Wallerian degeneration (WD). The NAD hydrolase, Sarm1, is required for the timely progression of WD. Sarm1 deficiency has recently been shown to enhance neuron intrinsic growth programs and axon regeneration in flies and worms. However, in the Wld^s mouse, delayed WD is associated with delayed axon regeneration. To investigate whether Sarm1 dependent WD is required for timely axon regeneration, adult wildtype (WT) and *Sarm1-/-* mice were subjected to sciatic nerve crush (SNC) injury. Primary DRG neurons from injured *Sarm1-/-* mice show enhanced neurite outgrowth compared to WT. However, the enhanced growth capacity of sensory neurons *in vitro* was not associated with increased regeneration of $SCG10^+$ sensory axons *in vivo* at 7 days post SNC. We hypothesized

that changes within the nerve microenvironment contribute to this delay. In the current study, immunofluorescence staining showed that Schwann cell (SC) differentiation into $p75^+$ repair (r)SC was impaired in the distal stump of *Sarm1-/-* nerves. Western blot analysis at 1-, 3-, 7-, 14- and 21-days post SNC showed that rSC differentiation is delayed and more transient than in parallel processed WT nerves. To better understand whether the delayed appearance of rSC contributes to poor axon regeneration, we developed a double crush injury model in which injured sciatic nerves were subjected to a second SNC 10 days after the first injury to assay axon regeneration in the distal nerve where rSC are present in WT and *Sarm1-/-* mice. Reprograming of rSC in the double SNC *Sarm1-/-* distal nerve was confirmed by upregulation of rSC associated genes at the mRNA and protein levels, including p75, sonic hedgehog, and c-jun. Regeneration of sensory axons into the *Sarm1-/-* distal stump 3 days after double SNC was improved compared to *Sarm1-/-* nerves 3 days after single SNC but was reduced compared to WT mice subjected to double SNC. Flow cytometric analysis showed that innate immune cell infiltration into the *Sarm1-/-* double SNC distal nerve remained impaired compared to parallel processed WT nerves and was associated with an accumulation of myelin proteins, MBP and P0, observed by western blot analysis. These results suggest that while *Sarm1* deficiency may enhance the intrinsic regenerative capacity of peripheral neurons, timely progression of WD is required to generate a growth permissive environment composed of rSC and immune cells that contribute to the removal of fiber debris.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

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Program #/Poster #: PSTR264.04/S3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Intramural program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH).

Title: Lysosomal cholesterol hyperactivates mTORC1 contributing to pathogenesis in a CLN1 disease model

Authors: *A. P. APPU[1], M. B. BAGH[2], N. PLAVELIL[3], A. MONDAL[2], T. SADHUKHAN[2], A. LIU[2], A. B. MUKHERJEE[4];
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Abstract: The CLN1-disease, a devastating neurodegenerative lysosomal storage disorder (LSD), is caused by mutations in the *CLN1* gene. *CLN1* encodes palmitoyl-protein thioesterase-1 (PPT1), which depalmitoylates S-palmitoylated proteins (constituents of ceroid lipofuscin). Despite this discovery, the mechanism of CLN1 disease-pathogenesis has remained elusive. Recently, lysosomal cholesterol has been reported to activate mTORC1 kinase suppressing autophagy, which cause neurodegeneration in most LSDs. We found that in the brain of *Cln1*$^{-/-}$ mice, which mimic INCL, the lysosomal cholesterol level is significantly higher compared with that in their WT littermates. Intriguingly, in *Cln1*$^{-/-}$ mice, the level of Niemann Pick C1 (NPC1) in lysosomal fractions was significantly lower compared with that in their WT littermates. Moreover, NPC1 requires dynamic S-palmitoylation for trafficking to the lysosomal surface and in *Cln1*$^{-/-}$ mice, lack of Ppt1 misrouted NPC1-protein to the plasma membrane instead of its normal location on lysosomal membrane. Further, we found that Ppt1-deficiency in *Cln1*$^{-/-}$ mice lack of dynamic S-palmitoylation of NPC1 prevented its handover from adapter protein-2 (AP-2) to AP-3. Consequently, NPC1 was not transported to lysosomal membrane and misrouted to the plasma membrane. Along with this defect, the level of oxysterol binding protein (OSBP) and its anchoring proteins-VAPA and VAPB mediated increased cholesterol on lysosomal limiting membrane mediating mTORC1-activation, which suppressed autophagy. To determine whether inhibition of OSBP may rescue autophagy, we treated cultured CLN1 disease lymphoblasts and *Cln1*$^{-/-}$ mice with a pharmacological inhibitor of OSBP, OSW1. The results showed a significant suppression of activated mTORC1-markers, pS6K1 and p4E-BP1 and autophagy markers, LC3B and p62 in both CLN1 disease lymphoblasts and in *Cln1*$^{-/-}$ mice treated with OSW1. Importantly, we found that pharmacological inhibition of OSBP suppressed mTORC1 activation, rescued autophagy and protected the neurons in the brain of *Cln1*$^{-/-}$ mice. Our findings uncover a previously unrecognized role of *Cln1/*Ppt1 in lysosomal cholesterol homeostasis and reveal a novel targetable pathway for CLN1 disease.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.05/S4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Cuprizone-induced demyelination in the mouse - Immnunohistochemical characterization

Authors: *E. ESNEAULT, C. RONDEAU, S. COTTEREAU, S. PEDRON, F. SIMON; Porsolt, Le Genest St Isle, France

Abstract: Multiple sclerosis (MS), an auto-immune disease, is the most common disabling pathology in the young adult. Occurrence of plaques and demyelination are some hallmarks of this auto-immune disease and are mainly observed in the brain, optic nerves and spinal cord.

While advances in the understanding of the physiopathology of MS and in the treatment of relapsing disease have been made, there is still a need to improve the current therapies and find effective treatments to counteract the progression of the disease. This emphasizes the utility of translational animal models to evaluate new therapeutic approaches. The Cuprizone model is one of the more common MS models used to induce oligodendrocyte apoptosis at an early stage and demyelination after several weeks of exposure. The aim of the experiment was to determine functional and histopathological hallmarks of the cuprizone model in the mouse. C57/BL6 mice were fed with Cuprizone at 0.2% during 5 consecutive weeks. Time-course behavioral assessment was performed. The mice were evaluated in the rotarod and beam walking tests for motor coordination, in the wire hang test for muscular strength assessment and in the electronic Von Frey test for allodynia evaluation. Brains as well as spinal cords were collected at the end of the experiment for immunohistochemistry (IHC). Neuroinflammation and demyelination were assessed in different brain regions and at several spinal cord levels. The results showed that motor and muscular strength performances were not affected in cuprizone-intoxicated mice over the 5 weeks while a loss of body weight was observed. Pain sensitivity level evaluated by tactile allodynia was also not modified. An increase of Iba1 and GFAP immunostaining in the corpus callosum, and to a lesser extent in the cortex, were detected by IHC analysis. This was accompanied by a decrease of MBP immunostaining in the corpus callosum as well as in the cortex, suggesting a diffuse demyelination both in the white matter and in the gray matter. No clear effects were observed on Iba1, GFAP and MBP immunostaining in the spinal cord. Microglial and astrocyte activation followed by demyelination are the main histopathological hallmarks during the early phase of MS. The cuprizone model can therefore be a useful and predictive model for evaluating the potency of a new test item to induce remyelination, or its potency to accelerate an ongoing remyelination, following cuprizone intoxication.

Disclosures: **E. Esneault:** None. **C. Rondeau:** None. **S. Cottereau:** None. **S. Pedron:** None. **F. Simon:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

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Program #/Poster #: PSTR264.06/S5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Intramural program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)

Title: Inactivating mutations in the CLN1 gene dysregulate ER-Golgi trafficking of proteins causing ER-stress in CLN1 disease

Authors: *N. PLAVELIL, A. P APPU, A. MONDAL, A. B MUKHERJEE;
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Abstract: Inactivating mutations in the *CLN1* gene encoding a depalmitoylating enzyme, palmitoyl-protein thioesterase-1 (PPT1). Although *Cln1*$^{-/-}$ mice, which mimic human CLN1 disease, manifest ER-stress leading to neuronal apoptosis the mechanism underlying this defect has remained elusive. The newly synthesized proteins are transported from the ER to the Golgi via COPII vesicles. We tested a hypothesis that PPT1-deficiency impairs ER-Golgi transport causing ER-stress. We found that the levels of COPII-associated proteins are significantly higher in *Cln1*$^{-/-}$ mice compared with those in their WT littermates. Moreover, the level of these proteins in purified ER-fractions from *Cln1*$^{-/-}$ mouse brain was also elevated. We found that COPII proteins (e. g. Sec31A, Sec23A and Sec24A) require dynamic S-palmitoylation for their trafficking from the ER to Golgi. Intriguingly, in *Cln1*$^{-/-}$ mice, a reliable animal model of human CLN1 disease, the interaction of Sec23A and Sec24A with Sar1, required for COPII vesicle-formation, was significantly higher compared with those in WT littermates. The level of Sar1-GTP (active), which facilitates the export of proteins from the ER to the Golgi, was also increased in *Cln1*$^{-/-}$ mouse brain. To confirm this finding, we performed colocalization studies using cultured fibroblasts from CLN1-disease patients. The results showed that in CLN1-disease fibroblasts virtually all COPII-proteins except Sec13, a non-palmitoylated protein, were accumulated at a higher level in the ER compared with that in normal fibroblasts. Since CLN1 disease causes ER-stress and our results showed defective anterograde trafficking, we sought to determine the level of CLN8 in the ER. Remarkably, the levels of CLN8 in isolated ER fractions, were significantly higher in *Cln1*$^{-/-}$ mice compared with those in their WT littermates. Furthermore, the higher ER-localization of CLN8 in CLN1 disease-fibroblasts correlated with markedly lower colocalization with the Golgi-marker. Taken together, these results demonstrate that anterograde (ER-Golgi)-trafficking of proteins is defective in CLN1 disease. Our findings reveal a previously unrecognized function of *Cln1*/Ppt1 in ER-Golgi trafficking of proteins and explain, at least in part, a mechanism underlying ER-stress in CLN1-disease.

Disclosures: **N. Plavelil:** None. **A. P Appu:** None. **A. Mondal:** None. **A. B Mukherjee:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

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Program #/Poster #: PSTR264.07/S7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS F32 1F32NS122997-01
NINDS R01 5R01NS115488-02
NMSS Collaborative MS Research Centers

Title: Anti-myelin immunoglobulins from patients with multiple sclerosis may contribute to myelin pathology independently of demyelination

Authors: *A. S. LAPATO[1], K. GIVEN[1], N. J. JAHAHN[1], G. OWENS[2], J. L. BENNETT[3], W. B. MACKLIN[1];

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Abstract: Multiple sclerosis (MS) patients acquire temporally disseminated demyelinating lesions that frequently do not repair. One under-examined mechanism of remyelination failure in MS may be persistence of immunoglobulins (Igs) after initial demyelinating injury. Using our ex vivo murine organotypic cerebellar demyelination/remyelination culture model, we show that myelin-binding recombinant IgGs (rAbs) cloned from MS patient intrathecal B cell repertoires hamper remyelination independently of complement activation. In this system, the myelin formed during remyelination in the presence of MS rAbs displays various abnormalities, including outfolding and lack of association with remaining axons, at a rate greater than control. Glutathione-S-transferase π immunoreactivity was less frequent among CC-1+ post-mitotic oligodendroglia in MS rAb-treated cultures, suggesting that MS rAbs are sufficient to impede oligodendrocyte maturation (n=25-40 folia). To understand this system, we investigated the effect of myelin-binding MS rAbs specifically on oligodendrocytes, studying differentiating primary rat oligodendrocyte precursor cells (rOPCs). When oligodendrocytes were differentiated as primary cells on cover slips in the presence of MS- or isotype control- rAbs, myelin-binding MS rAbs stimulated higher per cell myelin protein immunoreactivity relative to control rAb or vehicle, suggesting dysregulated myelination. MS rAb binding was associated with more robust phosphorylation of the Src family kinase, Fyn, which has been shown to drive myelination in vivo. However, MS rAb-treated cells also showed various membrane derangements, with a subset displaying dramatic labyrinthine membrane topology enriched for the microtubule associated protein, Tau. Tau+ membrane inclusions were immunoreactive for the hyperphosphorylated moiety typically seen in the context of tauopathy, suggesting aberrant signaling (n=30-60 cells). Intriguingly, when rOPCs were differentiated on inert 2 µm nanofibers, cells made fewer wraps and had shorter average wrap lengths in the presence of MS rAb relative to control (n=15-40 cells). Together, these data suggest that Ig deposition alone may interfere with myelin repair in MS, representing a heretofore under appreciated mode of remyelination failure.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH-NINDS R01 NS065808
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Legacy of Angels Foundation
the European Leukodystrophy Association

Title: The pathogenic contribution of galactosylceramidase to late onset demyelination in the mouse and human brain

Authors: *N. SALDIVIA, D. ZELADA, J. WHITEHAIR, G. J. HELLER, M. I. GIVOGRI, E. R. BONGARZONE;
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Abstract: The mechanisms underpinning adult brain demyelination in disorders such as Multiple Sclerosis (MS) are largely unclear. A cosmos of genes has been identified in GWAS studies as genetic risk factors, which in addition to environmental insults such as viral infections may lead to increased white matter vulnerability. Our research largely uses models of lysosomal storage diseases, as these provide excellent experimental models to test basic biological hypotheses. Krabbe disease (KD) is an autosomal recessive leukodystrophy caused by mutations in the lysosomal enzyme galactosylceramidase (GALC). Despite of being very distinct, KD bears some parallelism with MS. For example, GALC variants have been proposed as risk factors in MS, both conditions undergo neuroinflammatory demyelination, and both develop neuronal deficits. In KD, the toxic accumulation of galactosylsphingosine (psychosine) metabolite occurs owed to GALC deficiency, leading to an early onset of rapid and diffuse demyelination of white matter. This can largely be prevented using our gene therapy protocol with AAV9-GALC vectors delivered to newborn GALC deficient pups (Twitcher, TWI). Gene therapy normalized GALC activity, and significantly ameliorated central and peripheral neuropathology, with a significant extension in lifespan, and importantly, preservation of functional white matter in the brain for several months after treatment. However, as treated TWI mice aged, multiple focal demyelinating areas developed in white matter areas in their brains. These lesions showed deficits of GALC and elevation of psychosine content, in sharp contrast to neighboring normal-appearing white matter. Lesions were surrounded by inflammatory gliosis and affected by extravasation of fibrinogen from near blood vessels. Due to the similarity in the neuropathological presentation with demyelinating plaques observed in MS, we hypothesize that adult dysfunction of GALC metabolism in MS patients may contribute to local deficiencies in brain white matter and enhance vulnerability to demyelination. We are testing this hypothesis by determining GALC metabolic status of demyelinating plaques in human MS tissue.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

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Program #/Poster #: PSTR264.09/S9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH-NINDS F99NS125815

Title: Moderation effects of cumulative hair cortisol and self reported stress on the relationship between brain atrophy and cognition in a diverse multiple sclerosis sample

Authors: *S. MOODY[1], M. MANUEL[2], J. LOVERA[3], B. COPELAND[3], A. A. WILLETTE[4], E. SHIRTCLIFF[5], D. DEVIER[6];
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Abstract: Exacerbation of symptoms in Multiple Sclerosis (MS) due to stress are documented for both onset and relapse. Social stressors are linked to early age of MS onset for individuals with high adverse childhood experience scores. The association between dampened and elevated cortisol levels and MS outcomes, as well as mutations in glucocorticoid receptors predicting both the likelihood of diagnosis and severity of MS indicates stress's role on a biological level as well. Race and sex are explicitly linked by way of social stressors and predict onset, severity, and mortality of MS. Despite the cumulative effect on stress and the differences in MS at the intersection of race and sex, few studies have examined how markers of stress impact MS in the context of race and sex. To examine this gap, we used regression models to test whether the relationship between brain atrophy (third ventricle width: 3VW) and clinical outcomes of MS are moderated by biological (e.g., cortisol) and psychosocial (e.g., perceived social stress: PSS) markers of stress. Black (N=47) and White (N=58) non-Hispanic MS patients, age (M: 45.87, R: 19-71, SD: 12.96) were recruited from the U.S. in the gulf coast region. Participants completed cognitive (e.g., symbol digit modalities test: SDMT) and physiological (e.g., Expanded Disability Status Scale: EDSS | MS Severity Scores: MSSS) assessments, questionnaires on demographics, reported experiences of stress, provided hair to assess cumulative levels of cortisol, and granted access to their clinical MRI scans.High cortisol was associated with worse scores on the SDMT [$F(1, 55) = 5.982$, $p = .018$], ($R^2 = [.098]$, $\beta = [-2.56]$) but when parsed by race, only remained in White participants [$F(1, 27) = 5.614$, $p = .025$], ($R^2 = [.172]$), $\beta = [-3.608]$). High cortisol was also associated with larger 3VW [$F(1, 38) = 7.236$, $p = .011$], ($R^2 = [.16]$, $\beta = [.511]$) and again only remained significant for White participants [$F(1, 24) = 11.866$, $p = .002$], ($R^2 = [.331]$) ($\beta = [.740]$).
Cortisol only moderated the relationship between 3VW and SDMT in Black participants [$F(3, 8) = 3.938$, $p = .040$], (▲ $R^2 = .301$), such that high cortisol and larger 3VW were associated with poorer SDMT scores. PSS only moderated the relationship between 3VW and SDMT in Black participants [$F(3, 7) = 2.28$, $p = .046$], (▲ $R^2 = .375$), such that participants with low levels of PSS and large 3VW were associated with lower SDMT scores. Black participants with high PSS showed little difference in SDMT performance regardless of large or small 3VW. These findings suggest that the impact of biopsychosocial indices of stress on clinical outcomes of MS may differ based on the race of an individual.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.10/S10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: STAT3 siRNA-encapsulated PLGA nanoparticles mitigate experimental autoimmune encephalomyelitis by inhibiting immune cell infiltration.

Authors: T. KWON[1], Y. SEO[2], I.-H. CHO[2];
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Abstract: Background: Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that is activated by cytokines and growth factors. Expression of STAT3 is increased in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE). It contributes to peripheral-derived immune cell infiltration, demyelination and neuroinflammation. Therefore, regulation of STAT3 expression is expected to play an important role in disease improvement in MS and EAE. **Methods:** In this study, effectiveness of STAT3 siRNA-encapsulated PLGA nanoparticles (5, 10 and 20 mg/ml) in EAE was investigated using a rodent model of MS. **Results:** Inhibition of STAT3 with P-siSTAT3 at the onset point ameliorated motor impairment in EAE mice. In particular, P-siSTAT3 improved symptoms of EAE associated with demyelination, infiltration and activation of immune cells (resident microglia, monocyte-derived macrophage), increased expression levels of inflammatory mediators (iNOS and COX-2), inflammatory cytokines (IL-1β, IL-6 and TNF-α) and chemokines (MIP-1α, MCP-1 and RANTES) in the lumbar spinal cord compared to the control. It also reduced the infiltration of $CD4^+$/IFN-γ^+ (Th1) and $CD4^+$/IL-17^+(Th17) cells into the lumbar spinal cord in EAE mice with downregulated mRNA expression levels of IFN-γ, T-bet, IL-17 and RORγt. Additionally, it preserved the integrity of the blood-brain barrier. These positive effects of P-siSTAT3 are expected to regulate inflammatory responses of resident microglia. **Conclusions:** P-siSTAT3 can alleviate EAE by preserving inflammatory responses and BBB integrity. These results suggest that P-siSTAT3 might have potential therapeutic implications in autoimmune demyelinating diseases such as MS through maintenance of BBB integrity.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

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Program #/Poster #: PSTR264.11/T1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Characterization of WD-910, a CNS-penetrant TYK2 Inhibitor for the treatment of CNS diseases

Authors: *N. WANG, M;
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Abstract: TYK2 (JH2, pseudokinase domain) is a key regulator of IL-12, IL-23 and type I interferons signaling pathways, which have been shown to be involved in the pathogenesis of multiple inflammatory and autoimmune diseases such as psoriasis, lupus, inflammatory bowel diseases (IBD), multiple sclerosis (MS), Parkinson's disease (PD), stroke, and Alzheimer disease (AD). Sotyktu™(deucravacitinib , BMS986165) blocks TYK2 signals and has been approved by FDA to treat adults with moderate-to-severe plaque psoriasis without toxicity potential and also is in phase III trial for lupus. Here, we report a potent CNS-penetrant oral TYK2 allosteric inhibitor, WD-910, with high selectivity and potency through optimized binding to the JH2 domain of the TYK2 protein. WD-910 inhibits IFNα triggered pSTAT5 potently in human whole blood assay. In addition, WD-910 has excellent selectivity against other JAK family kinases. Furthermore, therapeutic efficacy of WD-190 has been evaluated in an experimental autoimmune encephalomyelitis (EAE) mouse model that shares many features of human MS. The results show WD-190 significantly reduces the disease progress after starting its treatment at the peak of the disease even in low dose. In vivo pharmacodynamic study indicates that WD-910 significantly reverses IL12/18-induced IFNγ and Th17 development, decreasing IL-17, IL-22, and TNF-α production, with concomitant increase in Treg numbers, in mouse. WD-910 brain/plasma ratio has been evaluated by measuring brain and plasma concentrations to have outstandingly 1.3 ratio. In summary, WD-910 is a highly selective, potent and CNS-penetrant oral small molecule TYK2 inhibitor (JH2) exhibiting great therapeutics in CNS neuroinflammatory diseases, like MS, PD and AD.

Disclosures: N. wang: None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.12/T2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH F32NS122997-02
NIH R01NS115488
NMSS Collaborative MS Research Centers

Title: Exposure to Multiple Sclerosis Autoantibodies Impairs Remyelination

Authors: *G. PEET[1], A. LAPATO[3], B. FRIETZE[4], K. GIVEN[2], G. OWENS[2], J. L. BENNETT[2], W. B. MACKLIN[5];
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Denver, CO; [4]NMSU, Las Cruces, NM; [5]Dept Cell & Dev Biol., Univ. Colorado Med. Sch., Aurora, CO

Abstract: Multiple Sclerosis (MS) is an immune-mediated disorder of the central nervous system. Its pathogenesis is poorly understood. Myelin reactive antibodies are found in MS patient parenchyma and cerebrospinal fluid and treatments that target the antibody-producing B-cell compartment improve MS progression markedly. Still, the role of these antibodies in MS lesions remains largely obscure. We developed a novel mouse model of autoimmune demyelination of the central nervous system. MS patient-derived myelin-binding autoantibodies cause complement-mediated demyelination in the brain and in organotypic slice cultures. This model produces lesions characterized by massive oligodendrocyte cell death, microglial phagocytosis of myelin debris, and robust, but incomplete, remyelination. Interestingly, continued exposure to the autoreactive antibodies without complement during remyelination altered the quality of newly regenerated myelin, i.e., the production of more non-axon associated myelin, suggesting a deleterious role for myelin reactive antibodies beyond primary demyelination. We sought to understand if chronic myelin-reactive antibodies could cause remyelination failure in MS. We hypothesized that this remyelination failure could be caused by altered microglial function in the presence of myelin-reactive antibodies. Single-cell RNA sequencing of microglia from remyelinating cerebellar slices with or without chronic myelin-reactive antibody exposure revealed increased Gpnmb, a known modulator of myelination, as well as an interferon-responsive gene signature. To assess the relevance of increased Gpnmb expression, primary rat oligodendrocyte progenitor cells were cultured in the presence of 100 ng/mL GPNMB ectodomain. GPNMB increased O4+ oligodendrocyte density and induced integrin signaling via FAK and AKT in cells maintained in the OPC state but did not alter integrin signaling in differentiated oligodendrocytes. Treatment of remyelinating cerebellar slices with GPNMB did not reduce the quantity of mistargeted myelin noted above, but increased the quantity of myelin found on axons, suggesting GPNMB may improve myelination. Future work will dissect the contributions of microglial function and oligodendrocyte response driven by chronic exposure to myelin-reactive antibodies and seek to characterize these effects in vivo.

Disclosures: G. Peet: None. **A. Lapato:** None. **B. Frietze:** None. **K. Given:** None. **G. Owens:** None. **J.L. Bennett:** None. **W.B. Macklin:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.13/T3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R21 NS121141-01A1

Title: Subjective Vs. Objective Cannabis Use Grouping: Implications for Cross-Sectional Analyses in People with Multiple Sclerosis

Authors: *J. R. DETERS[1], L. L. BOLES PONTO[2], D. J. MOSER[3], J. KAMHOLZ[4], P. E. GANDER[2], T. RUDROFF[5];
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Abstract: α-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), constituents of *cannabis sativa*, are growing in popularity for Multiple Sclerosis (MS) treatment due to the purported medical benefits for symptoms such as pain and muscle spasticity. Regulation and oversight of medical cannabis products are currently not comparable to FDA-approved drugs, and unsurprisingly, variability in label accuracy for legally purchased medical cannabis products has been reported. Therefore, we sought to investigate whether this was the case in a community sample of people with MS (PwMS). PwMS (N=10) consuming legally purchased cannabis products reportedly containing THC and/or CBD for at least 6 months were recruited. Cannabis consumption habits were recorded. A blood draw was also performed on each subject at least four hours post last use to test for the presence/concentration of the main metabolites of THC (11-OH-THC, THC-COOH) and CBD (7-OH-CBD, 7-COOH-CBD). Additionally, brain glucose metabolism was assessed with Positron Emission Tomography using the glucose analog [^{18}F]-fluorodeoxyglucose. Standardized (to patient bodyweight) uptake values (SUV; g/mL) in addition to a relative regional metabolism value (RRM; normalized in reference to volume-weight global mean SUV) were calculated for brain regions known to have high concentrations of cannabinoid receptors (hippocampus, amygdala, basal ganglia, cingulate gyrus, cerebellum). These values were compared between groups using independent samples t-tests. When grouping by subject reporting (THC = 4, CBD = 3, THC+CBD = 3), there were no differences seen across all brain regions assessed, and only the right anterior cingulate gyrus approached significance when measuring RRM ($p = 0.09$). Importantly, plasma levels of THC and CBD metabolites in PwMS did not correspond with the reported product being consumed, and thus subjects were regrouped into CBD-only (N=3) and THC+CBD groups (N = 6; 1 subject had no CBD or THC metabolites). When the regions were re-analyzed with this objective grouping, the bilateral hippocampus and amygdala had higher RRM values in the THC+CBD group compared to the CBD-only group (i.e., increased metabolism; all $p < 0.04$). The right caudate nucleus, pallidum and posterior cingulate gyrus all were approaching significance but did not meet the threshold ($0.05 \leq p \leq 0.10$; THC+CBD group < CBD-only SUV in each region). This is significant, as much of the literature on cannabis does not objectively verify consumption. Thus, our data suggest that it is necessary to utilize objective verification methods for cannabis use, otherwise the validity of the results come into question with respect to actual drug usage.

Disclosures: J.R. Deters: None. **L.L. Boles Ponto:** None. **D.J. Moser:** None. **J. Kamholz:** None. **P.E. Gander:** None. **T. Rudroff:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.14/T4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Department of Defense (MS200232)
TEDCO Maryland Innovative Initiative (135025)

Title: TPPB modulates the activity of innate immune cells and alleviates the neurologic symptoms in EAE model

Authors: *S. SHANMUKHA, W. GODFREY, P. GHARIBANI, M. D. KORNBERG, P. M. KIM;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Multiple sclerosis (MS) is a chronic neuroinflammatory disorder of the central nervous system resulting in demyelination of axons and loss of neurons. Available MS therapies with limited potential, rises the need for novel therapies with improved efficacy, safety, and targeted mechanisms of action to address the complex nature of the disease. The current research is aimed to find neuroprotective potential of TPPB (2S,5S)-(E,E)-8-(5-(4-(Trifluoromethyl)phenyl)-2,4-pentadienoylamino)benzolactam), a cell-permeable high affinity protein kinase C (PKC) modulator, in experimental autoimmune encephalomyelitis (EAE) model of MS. EAE was induced by immunizing the C57BL/6 mice with myelin oligodendrocyte glycoprotein peptide (MOG35-55). In this study we show that TPPB could alleviate the neurological deficits of EAE when administered intraperitoneally (IP) at a dose of 25 μg/kg, three days per week at the onset of MS clinical signs. Furthermore, in vitro treatment of bone marrow derived macrophages with TPPB resulted in a significant reduction in interleukin (IL)-12 levels, as determined by enzyme-linked immunosorbent assay (ELISA), and a concomitant increase in IL-10 levels indicating that TPPB promotes an anti-inflammatory phenotype. In addition, flow cytometric analysis revealed that the therapeutic treatment with TPPB suppresses the central nervous system inflammation as shown by the reduction in the elevated population of CD11B+CD45+ cells in brain and spinal cord and CD4+/IL-17+ T cells in the spinal cord of EAE mice. There was increased the population of CD4+Foxp3+ regulatory T cells (Treg) cells in brain and CCD11B+CD45+CD206+ cells in the spinal cord of TPPB treated group suggesting a regulatory mechanism aimed at dampening the immune response in EAE. Overall, this study suggests that TPPB, through its activity on PKC, could modulate innate immunity and promote a regenerative activity in these cells, which will have a significant clinical implication in MS treatment.

Disclosures: S. Shanmukha: None. **W. Godfrey:** None. **P. Gharibani:** None. **M.D. Kornberg:** None. **P.M. Kim:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.15/T5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AG075069

Title: Distinct brain cellular responses to chronic low-level arsenic exposure in mice

Authors: *M. ALAM, N. F. FITZ;
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Abstract: Abstract: Arsenic (As) is a naturally occurring metalloid element that is both widely distributed in the environment and chronic environmental As exposure affects the health of millions of people worldwide. One of the major sources of As exposure is through ingestion of contaminated groundwater. Arsenic can easily pass blood-brain barrier, accumulating in brain and epidemiologic studies demonstrate associations between As exposure and cognitive deficits in children and poor global cognition in adults. However, much less is known about the underlying molecular and cellular mechanisms in brain associated with As exposure. Recently, we have shown that chronic low level (100 ppb) As exposure caused significantly diminished cognition in wild-type mice and in whole brain tissue presented with a unique epigenetic signature associated neurodegeneration. No studies have determined how As exposure impacts particular brain cell types. We hypothesize that arsenic induces complex pathophysiological signaling mechanisms between neurons and glial cells through epigenomic and transcriptional changes, impacting healthy brain aging. To test this, we treated C57BL/6 wild-type mice for 4 months with 100 ppb sodium arsenite via drinking water and compared them to mice on control drinking water. We performed CUT&TAG and RNA-seq on MACS sorted microglia ($CD11b^{+}$), astrocytes ($ACSA\text{-}2^{+}$) & neuron (negative selection) from cortical tissue of both groups. The initial results of our experiments show that the number of differentially expressed genes (DEG) ($p < 0.05$) in astrocytes (772 genes) and neurons (873 genes) is higher than microglia (208 genes) when comparing the As group to controls. The examination of gene ontology (GO) indicates higher number of significantly down regulated genes in astrocytes associated with lipid metabolic process, brain development, synapse assembly following As exposure. In neurons, down regulated genes in the As group were associated with lipid metabolism, immune system process, and inflammatory response. Assessment of histone modifications follow As exposure support the transcriptional signatures. This indicates pathological mechanisms in response to As exposure could accelerate susceptibility to neurodegeneration or modify normal brain aging.

Disclosures: M. Alam: None. **N.F. fitz:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.16/T6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: ARUK-2021 DDI-UCL

Title: Development of a functional cell-based assay and cellular thermal shift to screen for modulators of Phospholipase C-gamma 2, PLCG2.

Authors: *F. E. JEGANATHAN[1,2], L. MAGNO[2], E. MEAD[3], K. COSTELLOE[2], E. MURPHY[3], J. HENDERSON[3], F. SVENSSON[2], M. BICTASH[2], P. FISH[2], P. WHITING[2], P. BRENNAN[3], F. DUCOTTERD[2];
[1]Univ. Col. London, London, United Kingdom; [2]ARUK UCL Drug Discovery Institute, London, London, United Kingdom; [3]ARUK Oxford Drug Discovery Inst., Oxford, United Kingdom

Abstract: The PLCγ2 isoform is predominantly expressed in the immune and haematopoietic cells and is differentially regulated by receptor tyrosine kinases (RTKs) or non-receptor tyrosine kinases. It selectively hydrolyses 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate to secondary messengers' inositol-3-phosphate (IP3) and diacylglycerol. Genome Wide Association Studies (GWAS) have identified a novel coding variant (P522R) in the immune gene Phospholipase C-gamma 2 that is protective against the cognitive decline associated with late onset Alzheimer's Disease (LOAD) and identifying small molecules that target PLCγ2 is a novel therapeutic strategy for AD. To identify modulators of PLCγ2 we developed a B cell RAMOS assay, since the PLCγ2 pathway downstream of the B cell receptor is well characterised and complemented this with the **Ce**llular **T**hermal **S**hift **A**ssay®. PLCγ2 is the predominant PLC isoform in the RAMOS B cells and the protocol was optimised for use with cells in suspension. Reaction conditions were optimised to identify small molecule modulators of the B cell pathway using a biochemical IP1 HTRF endpoint as a readout of IP3 production. In the THP-1 macrophage cells, where PLCγ2 is highly expressed, the remaining intact PLCγ2 protein was measured after heat shock in the presence of compounds to determine that the compounds were either on target or proximal to PLCγ2 whilst eliciting the desired pharmacological profile. We used these approaches in parallel to screen a library of 20,000 diversity compounds and identified 62 potentiators that were concordant across both. The compounds were screened in single-point and selected compounds were run to determine EC_{50}. Cut-off criteria for failing plates were Z prime < 0.5 and CV>10%. B scoring normalisation was used to correct for plate and positional effects. % Effect was calculated over DMSO controls. These approaches identified novel modulators of the PLCγ2 pathway with an overall hit rate of 0.31%. We used functional and biophysical cell-based approaches to identify positive modulators of PLCγ2. This offered the advantage of identifying compounds engaging with the activated form of PLCγ2 in the cellular environment where the membrane, native substrate and other interacting partners of the complex are present. It is unclear how the PLCγ2 P522R variant exerts its protective effect but the higher PLC activity could be achieved by adopting a more stable active form or by enhanced interactions with regulatory proteins or membrane. The combination of these approaches allowed identification of novel modulators of the PLCγ2 pathway.

Disclosures: F.E. Jeganathan: None. **L. Magno:** None. **E. Mead:** None. **K. Costelloe:** None. **E. Murphy:** None. **J. Henderson:** None. **F. Svensson:** None. **M. Bictash:** None. **P. Fish:** None. **P. Whiting:** None. **P. Brennan:** None. **F. Ducotterd:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.17/T7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AG-063029
NIH Grant NS-124123

Title: Increased activity of IRE1 improves the clinical presentation of EAE

Authors: *V. BRACCHI-RICARD[1], K. NGUYEN[1], D. RICCI[2], B. GAUDETTE[2], J. HENAO-MEIJA[2], R. BRAMBILLA[3], T. MARTYNYUK[1], T. GIDALEVITZ[1], D. ALLMAN[2], J. R. BETHEA[1], Y. ARGON[2];
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Abstract: Activation of the ER stress sensor IRE1α contributes to neuronal development and is known to induce neuronal remodeling *in vitro* and *in vivo*. On the other hand, excessive IRE1 activity is often detrimental and may contribute to neurodegeneration. To determine the consequences of increased activation of IRE1α, we used a mouse model expressing a C148S variant of IRE1α with increased and sustained activation. Surprisingly, the mutation did not affect the differentiation of highly secretory antibody-producing cells but exhibited a strong protective effect in a mouse model of experimental autoimmune encephalomyelitis (EAE). Significant improvement in motor function was found in IRE1C148S mice with EAE relative to WT mice. Coincident with this improvement, there was reduced microgliosis in the spinal cord of IRE1C148S mice, with reduced expression of pro-inflammatory cytokine genes. This was accompanied by reduced axonal degeneration and enhanced CNPase levels, suggestiing improved myelin integrity. Interestingly, while the IRE1C148S mutation is expressed in all cells, the reduction in proinflammatory cytokines and in the activation of microglial activation marker IBA1, along with preservation of phagocytic gene expression, all point to microglia as the cell type contributing to the clinical improvement in IRE1C148S animals. Our data suggests that sustained increase in IRE1α activity can be protective *in vivo*, and that this protection is cell type and context dependent. Considering the overwhelming but conflicting evidence for the role of ER stress in neurological diseases, a better understanding of the function of ER stress sensors in physiological contexts is clearly needed.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.18/T8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Roche Intonate Project

Title: Analysis of neuropathology of multiple sclerosis brain using Akoya's PhenoCycler-Fusion Technology with particular attention to Epstein Barr Nuclear Antigen-1 and its related molecular mimics Including glialCAM, anoctamin-2, myelin basic protein, alpha-crystallin B, myocyte enhancer factor 2B

Authors: N. OR-GEVA[1], A. KHAN[2], C. RAPOSO[3], A. PRATAPA[2], B. TACKENBERG[3], R. PEDOTTI[3], N. MAMMADOVA[2], ***L. STEINMAN**[1];
[1]Stanford Univ., Stanford, CA; [2]Akoya Biosci., Menlo Park, CA; [3]F. Hoffmann-La Roche Ltd., Basel, Switzerland

Abstract: Epstein Barr Virus (EBV) has been identified as the trigger for multiple sclerosis (MS). Antibody to Epstein Barr Nuclear Factor-1 (EBNA1) is present in nearly 100% of patients with MS before the development of clinical symptoms appears. Infection with EBV is necessary, but not sufficient, for causation of disease. Within a region of fifty amino acids in EBNA1 are molecular mimics of portions of four molecules, GlialCAM, Anoctamin-2 (ANO2), Myelin Basic Protein (MBP), and alpha Crystallin-B (CRYAB). Immune responses via T cells and antibodies to these four molecules, play key roles in the pathogenesis of MS. These molecular mimics within EBNA-1 include portions of a channel protein ANO2, a chloride channel. GlialCAM is a chaperone of another channel protein, aquaporin 4 (AQP4). The third mimic in this hotspot of molecular mimicry includes portions of an abundant structural protein of myelin, MBP. The fourth notable molecular mimic is a portion of a small heat shock protein alpha-crystallin B, CRYAB. CRYAB has protective properties against neuroinflammation, and immunity to CRYAB exacerbates damage to the nervous system. Some of the peptide motifs contained in this region of EBNA-1 are congruent with similar motifs in the U24 protein of human herpes virus 6, and in the myocyte enhancer factor 2B, MEF2b. MEF2b, like EBNA-1 itself, is critical for maintaining the latency of EBV. Using Akoya's PhenoCycler-Fusion, an ultra-high multiplexed imaging system to interrogate 40+ biomarkers (including immune, neuronal, and viral markers) at the single cell level, allows unprecedented high dimensional profiling of MS tissue, revealing spatial locations of critical cells and molecules involved in the pathogenesis of MS. Using this method, the investigators have identified CD20 B cells in perivascular regions of MS brain expressing EBNA1 and latent membrane protein 1 (LMP1). Neuronal loss, microglial and astrocytic involvement are evident as is the presence of $CD4^+$ and $CD8^+$ T cells in the MS brain. This research highlights the importance of understanding the role of EBV and the potential of high-dimensional profiling techniques in unraveling the pathophysiology of MS.

Disclosures: **N. Or-Geva:** A. Employment/Salary (full or part-time):; Stanford University. **A. Khan:** A. Employment/Salary (full or part-time):; Akoya Biosciences. **C. Raposo:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **A. Pratapa:** A. Employment/Salary (full or part-time):; Akoya Biosciences. **B. Tackenberg:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **R. Pedotti:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **N. Mammadova:** A. Employment/Salary (full or part-time):; Akoya Biosciences. **L. Steinman:** A. Employment/Salary (full or part-time):; Stanford 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.; Roche. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Bristol Meyers Squibb, Atara Bio, NIH. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); None. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); None. F. Consulting Fees (e.g., advisory boards); Pasithea, 180 Life Sciences, BMS, Atara Bio.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.19/T9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Defense Health Agency

Title: Repeated occupational exposure to the pesticide methyl bromide causes changes in locomotor gait

Authors: *H. DAVIDSON[1,2,4], D. MCMEANS[1,3,4], E. A. PHILLIPS[4,5], M. J. SONNER[4,5], E. L. ROBERTS[4,5], J. L. STRICKER[4,5], H. I. WARWICK[4,5], K. A. FRONDORF[4,5], V. T. ETHRIDGE[4,5], N. M. GARGAS[4,5], J. G. ROHAN[4], S. H. ROMER[4,5];
[1]Wright State Univ., Dayton, OH; [2]Oak Ridge Inst. for Sci. and Educ., Oak Ridge, TN; [3]Oak Ridge Inst. for Sci. and Educ., Oak Ridge, OH; [4]Naval Med. Res. Unit Dayton, Dayton, OH; [5]Leidos, Reston, VA

Abstract: Methyl bromide is a colorless, nearly odorless, gas used to fumigate against insects, nematodes and rodents in agriculture and shipping. Methyl bromide is a neurotoxicant known to elicit neurological deficits from acute and chronic inhalation exposures. Although multiple clinical reports have shown methyl bromide induced neural deficits, the cellular and functional impacts of low-level occupational exposures have not been fully characterized. The primary objective of this study was to identify functional and anatomical changes from repeated exposure to methyl bromide. To achieve our objective, we used a nose-only exposure system to expose adult male Sprague Dawley rats to either room air, 50, 150, or 300 ppm of methyl bromide for 2 hours a day, 5 days a week for 4 weeks. The week following exposures, the rats were examined for voluntary locomotor gait changes, and significant changes in gait of multiple aspects of both the stance and swing phases of locomotor movement were observed. Likewise, we found a 10% increase in the base of support during voluntary locomotor gait suggesting additional stability requirements. Neuromuscular or cerebellar changes often underlie locomotor changes, so we analyzed the cerebellum, spinal cord, and neuromuscular junctions. We found approximately a 10% increase in reactive astrocytes in the cerebellum, but no glial changes in the ventral horn of the spinal cord where motoneurons are located. Interestingly, we also found a 14% increase in

denervated neuromuscular junctions in the extensor digitorum longus muscle of methyl bromide exposed rats. Collectively, our results suggest that repeated low-level inhalation of methyl bromide causes locomotor changes likely through central and peripheral altered mechanisms.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.20/T10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DOD CDMRP - PRARP grant W81XWH2010236
DOD CDMRP - GWIRP grant W81XWH2210488

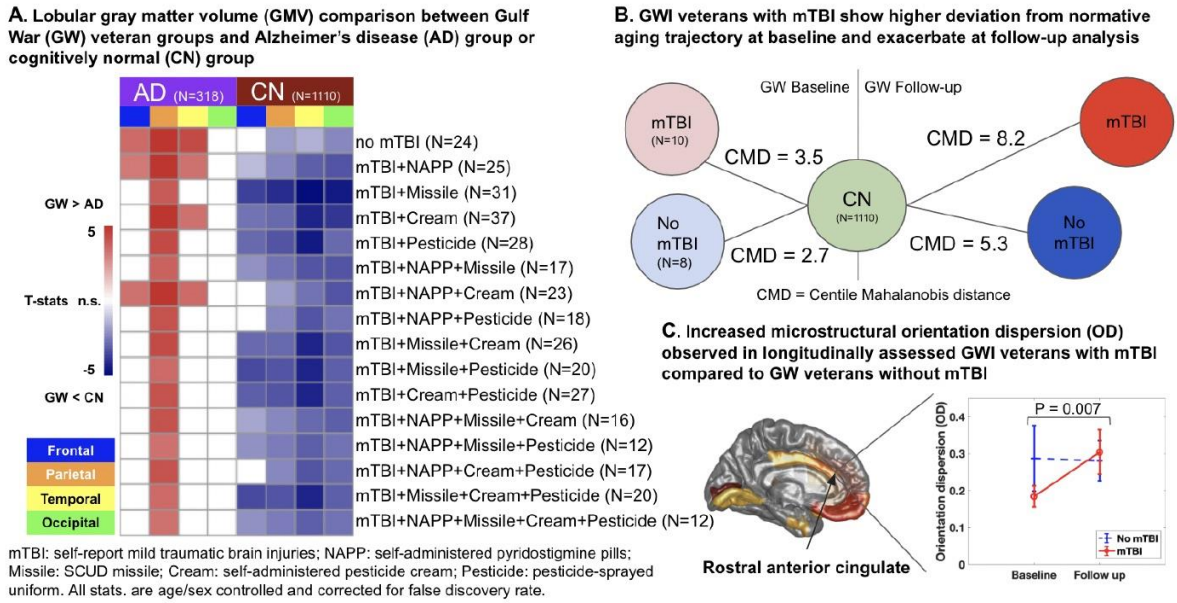
Title: Long-term effects of mild traumatic brain injury (mTBI) and toxicant exposures display accelerated pathological aging profiles: insights from structural and complex diffusion magnetic resonance imaging (MRI) analysis on Gulf War veterans

Authors: *C. CHENG[1], Y. GUAN[1], D. KIM[1], Y. OU[2], L. STEELE[3], K. SULLIVAN[4], B.-B. KOO[1];
[1]Anat. & Neurobio., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA; [2]Boston Children's Hospital, Harvard Med. Sch., Boston, MA; [3]Baylor Col. of Med., Houston, TX; [4]Boston Univ. Sch. of Publ. Hlth., Boston Univ. Sch. of Publ. Hlth., Boston, MA

Abstract: Thirty years after the 1990-1991 Gulf War, over one-third of the 700,000 U.S. Gulf War veterans (GWV) still suffer from Gulf War illness (GWI). Many of these veterans also experienced mild traumatic brain injuries (mTBI) during the war, and the combined impact of these injuries along with exposure to toxicants and stress may raise the risk of neurodegenerative conditions in the future. Given the emerging evidence suggesting that mTBIs may contribute to long-term pathological aging and increased risks of developing Alzheimer's disease (AD) (Barnes, 2018), here we investigate the aging profiles of GWV (N=166, 142 GWI, 134 males, 53±6.2 yrs.) in comparison to AD subjects (N=318, 179 males, 75.64±6.9), and cognitively normal (CN) subjects (N=1110, 510 males, 65.36±14.8). Based on gray matter volume (GMV) segmented with FreeSurfer (v6), we observed overall significant GMV reduction in GWV compared to the CN group, with more severe reduction seen in GWI veterans with mTBI and exposures (Fig.1A). Morphologically, GWI veterans with mTBI and exposures resembled the AD group in lower frontal and temporal volumes. In a subset of longitudinally assessed GWV (N=53, 43 GWI, 43 males), using a normative brain aging model on GMV showed increased cumulative deviation from baseline to follow-up in GWI veterans with mTBI compared to those without mTBI, indicating greater deviation of brain aging in this group (Bethlehem, 2022) (Fig.

1B). Further, longitudinal analysis on gray/white matter intensity ratio (GWR), which is known to decrease with aging (Salat et al., 2009), showed significant decreases (P=0.03, T=-2.44) in the rostral cingulate cortex in exposed GWI veterans with mTBI compared to their non-exposed, non-mTBI counterparts. Diffusion MRI analysis also displayed microstructural changes indicative of potential neuroinflammation in the same region (Cheng et al., 2020) (Fig. 1C). Overall, cross-sectional and longitudinal analyses using MRI measures demonstrated that toxicant exposures in GWI veterans may accelerate abnormal aging similar to AD, and was further exacerbated by mTBI.

Figure 1. Results overview



mTBI: self-report mild traumatic brain injuries; NAPP: self-administered pyridostigmine pills; Missile: SCUD missile; Cream: self-administered pesticide cream; Pesticide: pesticide-sprayed uniform. All stats. are age/sex controlled and corrected for false discovery rate.

Disclosures: C. Cheng: None. **Y. Guan:** None. **D. Kim:** None. **Y. Ou:** None. **L. Steele:** None. **K. Sullivan:** None. **B. Koo:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.21/U1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NINDS Grant NS114891
NIH NINDS Grant NS122918

Title: Neutrophil Extracellular Traps are Needed for Normal Myelin Clearance after a Sciatic Nerve Transection

Authors: *B. M. BALOG[1], J. P. NIEMI[1], T. J. DISABATO[1], R. E. ZIGMOND[2];
[1]Dept. of Neurosciences, Case Western Reserve Univ., Cleveland, OH; [2]Dept. of Neurosciences, Case Western Reserve Univesity, Cleveland, OH

Abstract: Neutrophils are required for normal Wallerian degeneration in the peripheral nervous system. This was demonstrated in *Ccr2* knockout (KO) mice, which have a reduced number of infiltrating macrophages, but normal myelin clearance. When neutrophils were inhibited with a Ly6G antibody after sciatic nerve transection, wild type (WT) and *Ccr2* KO mice showed reduced myelin clearance. Similarly, knockout mice for CXCR2, a receptor needed for neutrophil chemotaxis into the injured sciatic nerve have a reduction in neutrophil infiltration and myelin clearance. Neutrophils produce extracellular traps (NETs), which involve the release of chromatin outside of the cell, to aid in clearing pathogens. This process requires peptidyl-arginine deiminase 4 (PAD4) to citrullinate histone 3 (CitH3), so the DNA can decondense before being released outside of the cell. This is important as NETs are found in neurological disorders, but their purpose is not known. Using a peripheral nerve injury model, we investigated if NETs are required for normal myelin clearance. WT mice received a right sciatic nerve transection and the left served as an operated control. A PAD4 inhibitor or vehicle was injected into the nerve daily. Two days after the injury, animals were euthanized, and the tissue was fixed, sectioned, and stained for neutrophils (Ly6G), CitH3, and DAPI. Cell counts of Ly6G cells were not significantly different between vehicle or inhibitor groups, but the inhibitor group had a significant decrease in the number of Ly6G+, CitH3+, and DAPI+ NET structures compared to the vehicle group. Sections of nerves from animals treated for 7d after the injury were stained with luxol fast blue to detect myelin clearance. The vehicle groups showed a significant decrease in the percent area stained in the distal injured nerve compared to the sham injured. There was greater clearance in the vehicle injured group than in the inhibitor injured group. These results suggest that NETs are required for normal myelin clearance after a peripheral nerve transection. This contradicts a recent publication that suggested NETs are inhibitory to myelin clearance after a sciatic nerve crush injury. We are currently comparing the effects of transection and crush of the sciatic nerves in WT mice.

Disclosures: B.M. Balog: None. **J.P. Niemi:** None. **T.J. Disabato:** None. **R.E. Zigmond:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.22/U2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: PRONACES-CONACYT Grant 194171
VIEP-BUAP 2021-2022 to CA in Neuroendocrinología (BUAP-CA-288).

Title: Effects of leuprolide acetate on gait parameters in a model of H-ABC disease: the taiep rat

Authors: *J. C. AHUMADA JUÁREZ[1], J. R. EGUIBAR[2], C. CORTES[2], V. H. HERNANDEZ[3], V. PIAZZA[4];
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Abstract: Tubulinopathies refer to a wide group of diseases affecting the central nervous system (CNS) with a mutation in tubulins. Particularly, mutations in the tubulin β 4A (TUBB4A) gene cause in humans leukodystrophy named the hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). Motor signs such as ataxia and gait disturbances are the leading cause of disability in humans with H-ABC. The *taiep* rats were obtained at Institute of Physiology of Benemérita Universidad Autónoma de Puebla, and they had a progressive motor syndrome whit tremor, ataxia, immobility episodes, epilepsy, and paralysis. *Taiep* rat is the first model of tubulinopathy of human H-ABC whit a point mutation in the tubulin β 4A gene with a similar alteration in MRI image. The aim of this study was to evaluate the effects of leuprolide acetate, an agonist of gonadotropin release hormone (GnRH), on gait parameters in adult male *taiep* rats. We evaluated eight male *taiep* rats divided into two groups each with four subjects. Control group receive an intramuscular injection of physiological saline solution a second group with the 10 µg/Kg dose of leuprolide acetate (Sigma Aldrich, USA). The stepping pattern were analyzed using Catwalk™ system (Noldus Technologies, The Netherlands), and we measured the support base, the speed, the stride length, the duration of support, the swing and stand phase durations, as well the stepping sequence.The administration of leuprolide acetate improved coordination between the limbs ($P<0.05$). gait speed ($P<0.05$), and decreased the stance phase and the base of support ($P<0.05$), the gait that are clearly improved. In conclusion, the use of GnRH agonist improves four of the gait parameters evaluated. This drug has been a potential tool for treatment in humans affected with H-ABC and other leukodystrophies or leukoencephalopathies.

Disclosures: J.C. Ahumada Juárez: None. **J.R. Eguibar:** None. **C. Cortes:** None. **V.H. Hernandez:** None. **V. Piazza:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.23/U3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Canadian Institutes of Health Research grant to DPM
Canadian Institutes of Health Research grant to FGF
John R. Evans Leaders Fund to FGF
Intramural grants from the D'Or Institute for Research and Education (IDOR) and Rede D'Or São Luiz Hospital Network
Queen's University - Research Initiation Grant to FGF

Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro to FGF
Conselho Nacional de Desenvolvimento Científico e Tecnológico to FGF
Webber Endowment in Alzheimer's Research Fund to GBF
Honorable Hugh F. Gibson Award in Alzheimer's Research to GBF
The Queen's Gang Award to GBF

Title: Characterization of oculomotor behavior parameters to measure neurological impairment in recovering COVID-19 patients

Authors: *G. B. DE FREITAS[1], F. K. SUDO[2], J. HUANG[1], B. C. COE[1], B. J. WHITE[1], R. YEP[1], H. C. RIEK[1], O. G. CALANCIE[1], I. C. PITIGOI[1], D. C. BRIEN[1], E. C. RODRIGUES[2], T. P. PINTO[2], D. O. L. DE FREITAS[2], F. N. FERREIRA[2], S. A. BRASIL[2], M. C. BRITO[2], J. P. PINTO[2], C. G. R. DOS SANTOS[2], P. MATTOS[2,3], S. T. FERREIRA[2,4,5], F. TOVAR-MOLL[2], F. G. DE FELICE[1,2,4], D. P. MUNOZ[1];
[1]Ctr. For Neurosci. Studies, Queen's Univ., Kingston, ON, Canada; [2]D'or Inst. for Res. and Educ., Rio de Janeiro, Brazil; [3]Inst. of Psychiatry, [4]Inst. of Med. Biochem. Leopoldo de Meis, [5]Inst. of Biophysics Carlos Chagas Filho, Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: COVID-19, caused by the SARS-CoV-2 infection, led to a global health crisis. Growing evidence suggests that unsettled inflammatory processes resulting from the disease leads to 45% of survivors experiencing unresolved symptoms at least 4 months post-infection, rising with case severity. Neurological-related issues range from loss of smell to stroke and may further exacerbate pre-existing conditions, potentially contributing to the future development of neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD). Based on the hypothesis that increased chronic inflammation in the body and brain during COVID-19 can lead to changes in brain function, we aim to use a non-invasive method to identify key behavioral markers to study the chronic neurological alterations associated with Long COVID-19.We recruited a Brazilian cohort of patients 6 months to 1 year after hospitalization caused by severe COVID-19 (N = 34, 58.8 +/- 9.5 y/o; 24 males, and 10 females) and a control age and sex-matched cohort who either had mild, asymptomatic, or no infection (N = 61, 56.6 +/- 14.4 y/o; 25 males, and 36 females). The control of eye movements (EM) is linked to several brain regions that often overlap with the pathophysiology of NDDs. Thus, the EM system can be used as a non-invasive tool to probe details of sensory, motor, autonomic, and cognitive function, assessing the integrity of these brain circuits through quantitative video-based eye-tracking analysis. Subjects performed the Interleaved Pro-Anti Saccade Task (IPAST) paradigm, which evaluates the inhibitory control. The color of a central fixation point informs participants to look towards a visual stimulus (pro-saccade) or away from it (antisaccade), direction errors in the antisaccade task (failure of saccade suppression) suggests deficits in the cognitive control. Patients recovering from severe COVID-19 made more antisaccade direction errors compared with controls (Cohen's d = 0.58, p = 0.02), had increased antisaccade reaction time (d = 0.33, p = 0.01) and displayed a trend for increased voluntary override time (d = 0.48, p = 0.06), required to correctly perform antisaccade trials. These results suggest impairment in the inhibitory control signals emanating from the frontal cortex and basal ganglia to the superior colliculus, which is similar to other NDDs. Task-related pupil and blink responses remained preserved in COVID-19 patients. Our findings may aid in understanding and addressing long-term COVID-19-associated neurologic disorders, potentially informing future treatments and improving patient follow-up by highlighting the disease's long-term neurological effects.

Disclosures: **G.B. De Freitas:** None. **F.K. Sudo:** None. **J. Huang:** None. **B.C. Coe:** None. **B.J. White:** None. **R. Yep:** None. **H.C. Riek:** None. **O.G. Calancie:** None. **I.C. Pitigoi:** None. **D.C. Brien:** None. **E.C. Rodrigues:** None. **T.P. Pinto:** None. **D.O.L. de Freitas:** None. **F.N. Ferreira:** None. **S.A. Brasil:** None. **M.C. Brito:** None. **J.P. Pinto:** None. **C.G.R. dos Santos:** None. **P. Mattos:** None. **S.T. Ferreira:** None. **F. Tovar-Moll:** None. **F.G. De Felice:** None. **D.P. Munoz:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.24/U4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Post-covid-19 patients exhibited decreased globus pallidus activity independent of fatigue status - an exploratory fdg-pet study

Authors: *Y. LUO[1], P. GANDER[2], Y. WANG[1], L. PONTO[2], T. RUDROFF[1];
[1]Dept. of Hlth. and Human Physiol., Univ. of Iowa, Iowa City, IA; [2]Dept. of Radiology, Univ. of Iowa Hosp. and Clinics, Iowa City, IA

Abstract: Persistent fatigue is the most common and debilitating symptom of post-COVID-19 syndrome (PCS), profoundly impacting people's quality of life following acute COVID-19. However, the underlying pathophysiological mechanisms of PCS fatigue remain unclear. Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) is a neuroimaging technique that can be used to study the neuropathophysiological underpinnings of PCS fatigue. Recent neuroimaging studies have reported metabolic alterations of the brain in post-COVID-19 patients, specifically, hypometabolism in the basal ganglia (BG), especially the globus pallidus (GP) area. This is significant as GP dysfunctions are also associated with fatigue in other neurological disorders (e.g., Parkinson's Disease). Therefore, the aim of this study was to investigate the influence of fatigue status on the GP activity in post-COVID-19 patients compared to a healthy normative database. Thirty-two post-COVID-19 patients (16 females) were recruited to undergo an FDG-PET scan in a single session. PCS fatigue was determined by Chalder Fatigue Scale (CFQ-11) ≥ 5. 16 subjects (age: 38.5 ± 14.3 years, 8 females) were included in the fatigued (FT) group (CFQ-11 Score: 8.1 ± 2.4). 16 subjects (age: 28.2 ± 8.2 years, 8 females) were included in the non-fatigued (NF) group (CFQ-11 Score: 1.4 ± 1.5). Time since infection was similar between groups (6.9 ± 4.8 and 8.5 ± 5.7 months, $p = 0.38$). Z-scores were then computed to determine the deviation of values for each subject from the normative database. A z-score of ≥ 1.96 or ≤ -1.96 for the GP suggested relative hypermetabolism or hypometabolism, respectively, compared to the normative database. Hypometabolism was observed in the GP in both the FT ($z = -2.16 \pm 0.4$) and NF ($z = -2.65 \pm 0.4$) groups relative to the healthy normative database. A group (NF vs FT) × hemisphere ANOVA revealed no significant interaction ($F = 0.2$, $p = 0.65$). However, a main effect of group was observed ($F = 21.1$, $p < 0.001$) as the NF group demonstrrated greater GP hypometabolism (post-hoc $p < 0.001$,

d = 1.06). Additionally, a hemisphere main effect (F = 14.3, $p < 0.001$) showed higher z-scores for the right GP in both the FT (left z = -1.93 ± 0.4 and right z = - 2.28 ± 0.5; post-hoc $p < 0.001$, ***d*** = 0.76) and NF groups (left z = -2.36 ± 0.4 and right z = -2.8 ± 0.4; post-hoc $p < 0.001$, ***d*** = 1.17). Other BG regions did not differ from the normative database (≥1.96 or ≤-1.96). Our preliminary findings showed decreased GP activity at rest in post-COVID-19 patients independent of fatigue status, indicating that other potential factors (e.g., neuroinflammation, hypoxia, stress, anxiety, depression) may contribute to reduced glucose uptake in the GP.

Disclosures: Y. Luo: None. **P. Gander:** None. **Y. Wang:** None. **L. Ponto:** None. **T. Rudroff:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.25/U5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NCATS grant UH3TR00943-01
NCI grants 1R01CA182905-01
NCI 1R01CA222007-01A1
NIGMS 1R01GM122775-01
U54 grant CA096297/CA096300
CA160445P1
NIH grant CA200263
NCI R50 CA243707-01A1
NCI R37 1R37CA242006-01A1

Title: Degeneration of tumor associated nerves promotes resistance to anti-PD-1 therapy in cancer

Authors: *M. AMIT, J. MYERS, E. N. BARUCH, P. NAGARAJAN, F. O. GLEBER-NETTO, X. RAO, T. XIE, S. AKHTER, A. ADEWALE, B. J. MATTSON, R. FERRAROTTO, M. K. WONG, M. A. DAVIES, J. SONALI, B. SREYASHI, N. J. AJAMI, R. P. GOEPFERT, J. WANG, G. A. CALIN, M. R. MIGDEN, J. K. BURKS, J. GOMEZ, P. M. DOUGHERTY, J. P. ALLISON, P. SHARMA, J. WARGO, N. D. GROSS;
M.D. Anderson Cancer Ctr., houston, TX

Abstract: The nervous system has reciprocal interactions with both cancer and the immune system, however, little is known about the potential role of tumor associated nerves (TANs) in modulating anti-tumoral immunity. Here, we analyzed tumor samples of head and neck squamous cell carcinoma (HNSCC) patients who underwent neoadjuvant anti-PD-1 therapy. One third of the patients presented with invasion of cancer cells to TANs, and this invasion was associated with resistance to anti-PD-1. RNA sequencing data of The Cancer Genome Atlas data,

showed that invasion to peripheral nerves is associated with a neurodegeneration on Gene Set Enrichment Analysis (GSEA) and poor outcome. Using electron microscopy and electrical conduction studies, we showed that cancer cells can destroy myelin sheet and induce TANs degeneration. Multi-omics and spatial analyses demonstrated that anti-PD-1 non-responders had higher rates of TANs degeneration compared to responder, both at baseline and following the neoadjuvant treatment. Tumors from non-responders were characterized by a sustained signaling of interferon type I (IFN-I) in the tumor microenvironment- known to both promote nerve degeneration and suppress anti-tumoral immunity. Luminex analysis showed that neurons but not cancer cells, secrete INF-I and interleukin-6, upon stressful conditions in vitro. Spatial transcriptomic validated by high-plex immunofluorescence, showed that peri-neural niches of non-responders were characterized by higher immune activity compared to responders, including immune-suppressive activity of M2 macrophages, and T regulatory cells. This immune-suppressive infiltration expanded to the rest of the tumor microenvironment in non-responders. Anti-PD-1 efficacy was dampened by inducing nerve insult prior to treatment administration in syngeneic as well as humanized demyelination murine model of HNSCC. In contrast, anti-PD-1 efficacy was enhanced by denervation and by IFN-I or interleukin-6 blockade in-vivo. These findings suggested a potential novel anti-PD-1 resistance mechanism driven by cancer induced peripheral neurodegeneration with potential therapeutic implications.

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Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.26/U6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NEI R01 EY035053
NEI R01 EY028284

Title: The Immune Response to Prolonged Unilateral IOP Elevation in the Human Eye

Authors: *M. M. SOMERVILLE[1], M. GARNER[1], R. G. STRICKLAND[1], A. K. GROSS[1], C. A. GRIKIN[2];
[1]Dept. of Neurobio., [2]Ophthalmology and Visual Sci., Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Using an *in vivo* model of unilateral elevation in intraocular pressure (IOP) in research-consented brain-dead organ donors, our lab investigates the early cellular responses to acuteIOP elevation for the first time in the living human eye. We have found an increase of microglialreactivity regionally in the retina as well as in the posterior lamina cribrosa (LC) within the opticnerve head. Additionally, we have found regionally elevated astrocytic reactivity within theinferior and temporal LC, consistent with regions of greater susceptibility in glaucomatousneurodegeneration. Using immunohistochemistry in conjunction with in-situ hybridization, weare beginning to uncover the neuroinflammatory responses of the retina at the transcriptomiclevel and are targeting chemotactic ligand receptor expression levels as well as the expressionlevels of inflammatory cytokines and damage-associated molecular patterns (DAMP). Based onour preliminary data, we expect to find evidence to support a detrimental neuroimmunologicresponse that contributes to glaucomatous pathology.

Disclosures: M.M. Somerville: None. **M. Garner:** None. **R.G. Strickland:** None. **A.K. Gross:** None. **C.A. Grikin:** None.

Poster

PSTR264. Neuroinflammation and Neurological Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.27/U7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Subarachnoid haemorrhage leads to desialilation of hippocampal glycocalyx followed by complement system activation

Authors: *E. GOLANOV, A. REGNIER-GOLANOV, H. GOODWIN, N. KVIRKVELIA, R. LE, G. W. BRITZ;
Neurosurg., The Methodist Hosp., Houston, TX

Abstract: Subarachnoid haemorrhage (SAH) -- the accumulation of blood in the subarachnoid space - is the most fatal stroke, with a 40% mortality rate and 95% of survivors suffering permanent disabilities. Hippocampal neuroinflammation following SAH has been recognized as a potential cause of post-SAH syndrome, and the complement system (CS), in particular, has been identified as a major player. Levels of C1q, the activating protein of the classical pathway of the CS, are significantly higher in hippocampus (HPC) following SAH. However, mechanisms of C1q activation, the first step in CS activation, remain unknown. Our earlier data demonstrated that SAH-induced neuroinflammation, involves activation of astro- and microglia, leading to synaptic loss. While neuroinflammation of HPC involves activation of CS, specific mechanisms of its activation remain unknown. We hypothesize that damage of perforant pathway connecting blood exposed entorhinal cortex and HPC triggers release of sialidase and subsequent “trimming” of terminal glycocalyx - sialic acid (SA) - exposing potential binding sites for C1q and activation of the CS cascade. To test this hypothesis in perforation of the Willis circle model of SAH, we employed immunohistochemical staining using various lectins to detect

changes in sialylation and sialidase inhibitor (SI) treatment to explore changes in the hippocampal layers in SAH and Sham mouse brains. Levels of C1q increased significantly in the hippocampal molecular layer and stratum lacunosum moleculare ($P<0.002$ and $P<0.03$, resp. $n=6$) following SAH (areas of perforant pathway termination). Calculation of C1q/SA immunostaining ratio showed an increase ($P<0.005$, $n=3$) ratio in SAH versus Sham animals suggesting increased C1q binding due to cleavage of SA. Cleavage of terminal SA was confirmed by increased exposure of β-Galactose and N-acetyl-galactosamine ($P<0.04$, $n=3$, $P<0.005$, $n=3$, resp.) after SAH. Intra ventricular administration of SI reversed hippocampal synaptic loss ($P<0.0004$, $n=6$). Slice treatment with exogenous SI resulted in ($P<0.02$, $n=4$) higher levels of SA in Sham than in SAH animals. Our findings suggest that desialylated glycans form a substrate for C1q binding and its subsequent activation respective activation of innate complement system.

Disclosures: E. Golanov: None. **A. Regnier-Golanov:** None. **H. Goodwin:** None. **N. Kvirkvelia:** None. **R. Le:** None. **G.W. Britz:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.01/U8

Topic: C.08. Ischemia

Support: U.S. Dept. of Veterans Affairs; # 1IO1 BX004884

Title: Hexokinase-2 (HK2) inhibition attenuates pro-inflammatory gene expression by microglia / macrophages in peri-infract cortex as assessed by digital spatial profiling.

Authors: *G. URUK, S. WON, K. ARKELIUS, N. SINGHAL, C.-L. TU, W. CHANG, R. SWANSON;
Univ. of California San Francisco, San Francisco, CA

Abstract: Brain ischemia, infection, tissue injury, and other signals cause microglia and infiltrating macrophages (M/M) to become activated and release cytotoxic ROS and cytokines that may exacerbate brain injury. M/M exhibit a marked increase in glycolytic rate. Importantly, pro-inflammatory effects of activated M/M can be suppressed by limiting their glycolytic flux through inhibition of hexokinases. There are 4 isoforms of hexokinase, of which HK1 is the predominant isoform in most tissues whereas HK2 is the predominant isoform in cells of the M/M lineage. Availability of brain penetrating HK2-selective inhibitors provide a mechanism for selectively suppressing glycolytic rate in activated M/M. The aim of this study is to determine if HK2 inhibition can suppress pro-inflammatory gene transcription in M/M after permanent ischemia (photothrombotic stroke) in the mouse. HK2 inhibitors 3-bromopyruvate and lonidamine were administered i.p. after induction of permanent ischemia. We assessed pro-inflammatory gene expression changes in peri-infarct M/M and neurons using the DSP GeoMx

spatial genomics. This method allowed the entire M/M transcriptome to be analyzed in-situ with no need for isolation of them from brain, a process which itself causes some activation. This approach also enabled us to investigate the M/M at the infarct border and peri-infarct areas, preserving the crucial anatomical information and unaltered transcriptomic profile. Both HK2 inhibitors suppressed pro-inflammatory gene expressions such as ccl3, ccl4, cd14, plek, and hmox1 in peri-infarct M/M. Suppressing M/M HK2 activity thus provides a means for attenuated post-stroke activation of M/M at the transcriptional level.

Disclosures: **G. Uruk:** None. **S. Won:** None. **K. Arkelius:** None. **N. Singhal:** None. **C. Tu:** None. **W. Chang:** None. **R. Swanson:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.02/U9

Topic: C.08. Ischemia

Support: Dept of Veterans Affairs Grant # 1IO1 BX004884

Title: Hexokinase-2 inhibition reduces neuroinflammation-mediated brain damage after stroke

Authors: *S. WON, G. URUK, K. AWAKOAIYE, E. MOCANU, D. OGUT, R. SHON, N. SINGHAL, R. A. SWANSON;
VAMCSF & UCSF, San Francisco, CA

Abstract: Activated microglia can exacerbate brain injury after ischemic stroke through the innate immune response. Activated microglia also exhibit an increased glycolytic rate, and - crucially - the pro-inflammatory effects of activated microglia can be suppressed by limiting their glycolytic flux. Unlike other brain cell types, microglia (and macrophages) use primarily hexokinase-2 (HK-2) rather than hexokinase-1 to catalyze the initial step of glycolysis. HK-2 - selective pharmacological inhibitors are now available, thus providing a mechanism for selectively suppressing glycolytic rate in activated microglia / macrophages. The aim of this study is to determine if HK-2 inhibition can suppress pathogenic aspects of microglia / macrophage activation and improve the behavioral dysfunction after a model of permanent ischemia (photothrombotic stroke) in the mouse. The HK-2 inhibitors 3-bromopyruvate and lonidamine were administered i.p. after induction of permanent ischemia. Both drugs suppressed the morphological microglial activation, and by digital spatial profiling these drugs also suppressed pro-inflammatory gene expression in peri-infarct microglia. Histological studies showed reduced DNA-damage in peri-infarct neurons and reduced cofilin-actin rod formation in peri-infarct neurites in mice treated with the HK-2 inhibitors. Behavioral studies indicate reduced motor deficit in mice treated with 3-bromopyruvate after stroke. These results suggest that, by selectively suppressing glycolytic rate in activated microglia / macrophages after stroke, HK-2 inhibitors can improve outcome after permanent ischemia.

Disclosures: **S. Won:** None. **G. Uruk:** None. **K. Awakoaiye:** None. **E. Mocanu:** None. **D. Ogut:** None. **R. Shon:** None. **N. Singhal:** None. **R.A. Swanson:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.03/U10

Topic: C.08. Ischemia

Support: ERA-NET NEURON JTC 2019, 372 'STATEMENT', project code NEURON-082

Title: Identification of a blood biomarker of inflammation to predict the risk of ischemic stroke in atherosclerotic patients

Authors: *D. MERCURIO[1], L. MECHTOUFF[2], S. BELLAVIA[1], S. SEMINARA[1], A. BIANCHI[1], G. BIDAUX[3], M. BUISSON[4], T.-H. CHO[2], N. NIGHOGHOSSIAN[2], E. CANET-SOULAS[2], S. FUMAGALLI[1];
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Abstract: Ischemic stroke represents 87% of all strokes being a major cause of death and permanent disability worldwide. Atherosclerosis characterized by fatty deposits (plaques) in the inner walls of major arteries is the main risk factor for ischemic stroke. The lectin pathway (LP) of complement activation has pathogenetic functions in acute ischemic stroke, with implication in thromboinflammatory events. We reported that elevated circulating levels of the LP initiator ficolin-2 are associated with vulnerable atherosclerotic plaques, those that upon their rupture increase stroke risk. We here aimed at investigating ficolin-2 circulating levels after an acute ischemic stroke and their potential use as a biomarker able to differentiate stroke etiologies, namely atherosclerotic vs. others.300 patients (68.6y ± 16) were enrolled at Lyon Stroke Center for an acute ischemic stroke due to large vessel occlusion treated with mechanical thrombectomy. Blood was withdrawn at H0: admission, H6: hour 6, H24: hour 24, H48: hour 48, M3: month 3. Ficolin-2 circulating levels were measured by ELISA.Considering the whole cohort, circulating ficolin-2 levels were 5620 ± 2006 of ng/mL ± SD at H0 and decreased at H6 (4821 ± 1936, $p<0.001$ vs. H0), H24 (4928 ± 1811, $p<0.001$) and H48 (5182 ± 1851, $p<0.05$). Data indicate an early consumption of ficolin-2 after acute ischemic stroke, due to target binding and lectin pathway activation. A large-artery atherosclerosis (LAA) etiology regarded 40 patients (13%), showing lower circulating ficolin-2 at H6 (3810 ± 1775) compared to other causes of stroke (4971 ± 1917). The area under curve (AUC) reflected different ficolin-2 levels over time, namely AUC of 1.077e+007 ± 2997205 in stroke patients with LAA vs. 1.195e+007 ± 2914745 in those with other etiology ($p=0.02$, Unpaired t-test). Contingency analysis by Fisher's exact test showed that lower ficolin-2 levels at H0 and H6 were associated with LAA. Ficolin-2 levels

were seemingly independently associated with LAA since other risk factors including ASPECT score, obesity, dyslipidemia, coronopathy smoke, diabetes and hypertension were not.Our data indicate increased ficolin-2 usage in patients having a symptomatic atherosclerotic plaque, in line with the association of ficolin-2 circulating levels with vulnerable plaques. As such ficolin-2 circulating levels could predict the risk of stroke in atherosclerotic patients standing as a new biomarker with future diagnostic value to help develop stroke prevention and treatment.

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Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.04/V1

Topic: C.08. Ischemia

Title: Senescence Associated Secretory Phenotype (SASP) Influences the Stroke Outcome of Aged Mice

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Abstract: Ischemic stroke is a devasting brain injury and a leading cause of morbidity and mortality worldwide. While there is extensive research into stroke pathology, the effect of age, in relation to stroke severity has not been fully elucidated. Aging is a non-modifiable risk factor for stroke incidence and morbidity. In the aged brain, cells induce neuroinflammation through the activation of senescence associated secretory phenotype (SASP). Interleukin-1α (IL-1α), a pro-inflammatory cytokine is a major-upstream regulator of SASP and is heavily involved in the post-stroke inflammatory response. Additionally, ischemic stroke has also been found to induce SASP in the infarcted and periinfarct regions. However, the interplay between the already SASP-abundant aged brain and the impact on stroke may be worthy of elucidation. The study is aimed to understand the impact of proinflammatory cytokine, IL-1α, on the aged brain after stroke due to its dual involvement in post-stroke neuroinflammation and a critical upstream inducer of SASP. Middle cerebral artery occlusion was induced in young (9-week) and aged (16-month) mice, n=5/group, using the photothrombotic model. 30ul of Rose Bengal dye was injected retro-orbitally and the distal middle cerebral artery was laser illuminated for 10min. Brain was perfused and then hemispheres were harvested and fresh frozen separately for protein and mRNA analysis of markers of senescence and SASP expression. qPCR analysis of inflammatory, senescent, and SASP markers; IL-1α, IL-6, P16, P21, CXCR2, and CXCL1, found that there is inverse association of inflammatory and SASP markers with aged stroked mice comparing the young stroked groups. The aged sham showed higher senescent and SASP markers compared to young sham. Interestingly, while both age groups showed an increase in SASP marker in the

stroke versus sham, young stroke had significantly higher increase compared to even the aged stroke group and is further confirmed by immunofluorescence and western blot analysis. We found that there is increased SASP expression in the stroked ipsilateral hemisphere compared to the contralateral hemisphere in an age-dependent manner representing that there may be an inflammatory compensatory mechanism in the aged brain based on already present SASP expression. These results suggest that senescence and SASP are heavily integrated with stroke in an age-dependent manner and that the IL-1α SASP pathway may be a critical modulator of this phenomenon.

Disclosures: B. Ouvrier: None. **S. Ismael:** None. **G.J. Bix:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Program #/Poster #: PSTR265.05/V2

Topic: C.08. Ischemia

Support: Supported by Univ. of Pittsburgh Department of Neurology Start-up funding (GB)

Title: Astrocytic $Na^+/HCO3^-$ cotransporter 1 (NBCe1) in BBB damage in stroke mice

Authors: *O. CAPUK, S. SONG, S. METWALLY, G. BEGUM;
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Abstract: Astrocytes play a critical role in preserving the integrity and function of the blood-brain barrier (BBB). The perivascular astrocytic end-feet express a variety of channels and ion transporters that are crucial for maintaining ion and osmotic homeostasis, important for BBB functional integrity. Disruption of the BBB is a characteristic feature of ischemic stroke and contributes to the progression of neurodegeneration. Here, we investigated the role of electrogenic sodium bicarbonate transporter 1 (NBCe1/SLC4A4) in stroke-induced BBB damage. NBCe1 is predominantly expressed in astrocytes and plays important role in regulating brain pH homeostasis. Increased NBCe1 expression in reactive astrocytes correlates with neurological function impairment in ischemic stroke mice, yet the underlying mechanisms remain unclear. In our study, we used inducible *Gfap-Cre$^{ERT2+/-}$;Nbce1$^{f/f}$* mice to specifically delete NBCe1 in $GFAP^+$ reactive astrocytes. Astrocyte selective *Nbce1* deletion in *Gfap-Cre$^{ERT2+/-}$;Nbce1$^{f/f}$* (*Nbce1* cKO) mice displayed reduced infarct volume, brain swelling, and neurological function deficits at 1-7 days after ischemic stroke. Immunocytochemical analysis showed increased BBB damage and dysregulation of perivascular AQP4 polarity in wild-type ischemic brains. In contrast, *Nbce1* cKO brains exhibited improved BBB integrity, and preservation of perivascular AQP4 polarization and reduced loss of neuronal cells ($NeuN^+$ cells) at 3-day post-stroke. Furthermore, *Nbce1* cKO significantly increased regional cerebral blood

flow in the ischemic hemisphere at 3-day post-stroke. Taken together, our study provides the first line of evidence that pathological stimulation of astrocytic NBCe1 protein plays a role in ischemic BBB damage. These findings highlight the importance of astrocytes and NBCe1 in the pathogenesis of stroke and its potential as therapeutic targets for preserving BBB integrity in ischemic conditions.

Disclosures: O. Capuk: None. **S. Song:** None. **S. Metwally:** None. **G. Begum:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Topic: C.08. Ischemia

Support: Nebraska DHHS LB692
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Title: Inhibition of TREM1-mediated neuroinflammation attenuates global ischemic stroke pathology

Authors: *R. URQUHART, H. KIM, G. P. JADHAV, J.-Y. HWANG;
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Abstract: Global cerebral ischemia occurs when the blood flow to the entire brain is blocked or significantly impeded and is most often caused by cardiac arrest. Global ischemia induces delayed and selective hippocampal CA1 pyramidal neuronal death which leads to impaired learning and memory. Current therapies for cardiac arrest only focus on restoring cardiac function and blood flow - no treatments prevent long term effects of global ischemia. Thus, identifying the molecular mechanisms and therapeutic targets is essential for developing novel treatments to rescue global ischemia induced neuronal death and cognitive deficits. In this study, we sought to explore how dysregulation of genes might promote the neurodegeneration associated with global ischemia. Toward this end, we subjected rats to global ischemia via 4-vessel occlusion (4-VO) and performed RNA-seq to investigate alterations of mRNAs in post-ischemic CA1. Ingenuity Pathway Analysis showed the pathways related to inflammatory response including ‘neuroinflammation’ and ‘TREM1 signaling’ as the top canonical pathways. TREM1 is a myeloid-derived surface receptor involved in immunity and inflammation. TREM1 has known roles in myocardial ischemia and sepsis, but the role of TREM1 in global ischemia remains unclear. Based on our RNA-seq analysis, we hypothesized TREM1 mediated neuroinflammation drives global ischemia induced neuronal death and cognitive deficits, and TREM1 inhibition attenuates this pathology. RTqPCR and Western blot analyses revealed that TREM1 expression is elevated within 48HR of ischemia, and downstream inflammatory cytokines and transcription factors are also differentially expressed 3-48HR post 4-VO. These results validate RNAseq and IPA and confirm that TREM1 and its signaling cascade are

activated after global ischemia. To establish a causal relationship between TREM1 and global ischemia, the neuroprotectiveness of TREM1 inhibitory peptide LR12 was measured. LR12 administration reduced neurodegeneration in the hippocampal CA1 after ischemia, measured by histological staining, establishing LR12 as a neuroprotective peptide. Current experiments will address the hypothesis that LR12 prevents TREM1-mediated neuroinflammation, ameliorating global ischemia induced neuronal death and cognitive deficits. This research establishes the role of TREM1-mediated neuroinflammatory signaling in global ischemia pathology and identifies TREM1 as a potential therapeutic target for attenuating global ischemia-induced neurodegeneration and cognitive deficits.

Disclosures: **R. Urquhart:** None. **H. Kim:** None. **G.P. Jadhav:** None. **J. Hwang:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Program #/Poster #: PSTR265.07/V4

Topic: C.08. Ischemia

Support: CONACyT grant 663120

Title: Intranasal erythropoietin protects granular cells and reduces astrogliosis in the dentate gyrus after ischemic damage, an effect associated with molecular changes in erythropoietin and its receptor

Authors: *R. MACIAS-VELEZ, A. MARIN-LOPEZ, M. RIVERA CERVANTES;
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Abstract: Within the hippocampus, the CA1 and dentate gyrus (DG) regions are considered the most and the least susceptible to damage by cerebral ischemia, respectively. In addition, it has been tested that rHuEPO exhibits neuroprotective properties. The present study investigates the effect of different intranasal doses of rHuEPO, applied in different post-ischemic damage times in the DG, on the granular cell layer preservation as well as on astroglial reactivity after cerebral ischemia. Additionally, an effective dose and an administration time for neuroprotection were used to evaluate gene and protein expression changes of EPO and EPOR in the DG region. We observed a considerable loss of cells on the granular layer and an increased number of GFAP immunoreactive cells in this region 72 h after the onset of ischemic damage. When rHuEPO was intranasally administered, the number of morphologically abnormal cells and astroglial immunoreactivity decreased. Regarding to the protein and gene expression analysis, there is no correlation between the expression levels of these molecules, although the rHuEPO application amplifies the response of EPO and EPOR gene expression to ischemia in each evaluated time; in the case of protein expression, this effect was observed only 2h after damage. In summary, using a 2VO model in rats, we demonstrated that 20 min of bilateral occlusion are enough to detect a susceptibility of the DG to ischemic injury, which was observed in both granular cells alterations

and astrocytic response, which is accompanied by molecular changes on EPO and EPOR at particular post-damage times that might mediate the protective effect triggered by rHuEPO intranasal administration.

Disclosures: **R. Macias-Velez:** None. **A. Marin-Lopez:** None. **M. Rivera Cervantes:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Topic: C.08. Ischemia

Support: NIH R01 NS105905
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CU RBI Pilot Grant

Title: Rna-sequencing reveals inflammatory and synaptic structure pathways to differentially expressed after cerebellar stroke

Authors: G. HUNN, C. MINJAREZ, D. MITCHELL, M. MORENO GARCIA, *N. QUILLINAN;
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Abstract: More than 20,000 people suffer from cerebellar ischemic stroke yearly. Neuroimaging of the human cerebellum shows that an anterior lobule infarct produces motor deficits, while a posterior infarct likely leads to nonmotor deficits. Our rodent model injures the cerebellar cortex and emphasizes the same topographical deficits. However, there is a lack of knowledge of the mechanisms underlying the behavioral deficits seen in patients with cerebellar stroke. To further characterize this, we used deep cerebellar nuclei (DCN) and ventrolateral thalamus (VLT) tissue of stroke and sham brains to measure gene expression with bulk RNA-sequencing. This is because Purkinje cells in the cerebellar cortex project to the DCN, which is functionally connected to the VLT. Using photothrombosis, the superior cerebellar artery (SCA) was occluded in adult (8-16 wk) male C57/Bl6 mice. Infarcts were localized to the anterior (n=3) or posterior (n=3) regions of SCA or were shams (n=3). At 7 days post-stroke, DCN and VLT tissue was collected for RNA isolation and quality control. We did a PolyA preparation of RNA libraries and NovaSeq sequencing at a read depth of 30 million pairs per sample. Sequences aligned to the mouse genome and SALMON analysis produced gene counts. RStudio Principal Component Analysis revealed a large variation (85%) between the two regions and a small variation (9%) between the two types of strokes. We next focused on the DCN to assess the beginning of the circuit. DESeq2 analysis identified 239 differentially expressed (DE) genes in anterior compared to sham stroke, which consisted of 199 upregulated and 40 downregulated. Posterior compared to sham stroke produced 3621 DE genes in which 1966 were upregulated

and 1655 were downregulated. Using these genes, the Gene Ontology database showed an upregulation of inflammatory pathways in anterior compared to sham stroke. In addition to an upregulation of similar inflammatory pathways, posterior stroke mice also showed a downregulation in synaptic structure pathways. To validate our RNA-seq, immunohistochemistry assessed microglia activation. Imaris software showed a decrease in filament branch, along with an increase in soma volume and cell number, all indicating upregulation of microglia activation in anterior (n=4) and posterior (n=4) stroke compared to shams (n=4). Phagocytic activity of microglia measured with CD68 also increased in stroke compared to sham. Overall, while the DCN is not directly injured, this data identifies significantly different biological pathways in this brain region after cerebellar stroke, which led us to upregulated microglia activation that could contribute to functional changes.

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Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Topic: C.08. Ischemia

Support: CF-2023-G-289

Title: Determination of neuroinflammatory biomarkers in plasma of rats with acute global cerebral ischemia.

Authors: *O. MONTES[1], M. GARCÍA[1], O. GONZALEZ[1], R. J. DELGADO[2];
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Abstract: Cerebral ischemia (CI), is the most common type of stroke, representing more than 80% of all cases and accounting for 5.2% of all deaths worldwide. CI is characterized by decreased blood flow to the brain causing neuroinflammation and cell death. During postischemia neuroinflammation, interleukins (ILs) play a key role in the severity of brain damage. Some ILs such as IL-6 are known to be proinflammatory, in contrast, other ILs such as IL-10 have anti-inflammatory effects. The pharmacological modulation of both ILs and their detection in ischemic patients is a priority in the clinic; for these reason, in the present work, we propose the plasma detection of IL-6 and IL-10 at different postischemia times by using a novel technique known as attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR). The ATR-FTIR allows monitoring structural and concentration changes in biomolecules present in plasma samples quickly, inexpensively, without the need for sample preparation and using a small amount for detection. In this study we used male rats of the Sprague Dawley strain, these animals were included in an acute global cerebral ischemia (AGCI) protocol and their

blood plasma was obtained at; 0,2,4,6,12 and 24 hours after the ischemic event. Animals that received neuroprotective drug treatment were administered a single intraperitoneal dose of estradiol benzoate (EB) at a concentration of 4mg/kg. For the first statistical exploration of the data, we used the average values of each group obtained in the mid-infrared region (400-4,000cm-1) and principal component analysis (PCA) was performed. Our partial results show the highest plasma IL-6 concentration at 2 hours post-ischemia in animals that did not receive neuroprotective treatment, in contrast, the animals that received EB treatment showed low IL-6 levels at 2 hours and elevated IL-10 concentration at 6 hours post-ischemic event. The spectra obtained by ATR-FTIR measurements show different absorbance values, as well as modifications in the spectral peaks in the different experimental groups that are attributable to the pharmacological conditions of each group and to the time elapsed after the ischemic event. These results suggest that treatment with EB in ischemic individuals negatively modulates IL-6 proliferation in the acute phase of ischemia and, conversely, promotes IL-10 synthesis in the subacute phase of ischemia, in addition, we were able to standardize the methodology for the plasma measurement of IL-6 and IL-10 using (ATR-FTIR) and we characterized the plasma spectra of ischemic animals.

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Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Topic: C.08. Ischemia

Support: The National Research Foundation of Korea (NRF-2019R1A2C1087035 and 2022R1A2C1003564)
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Title: Noggin-induced changes in metabolism of microglia and oligodendrocytes after ischemic insult

Authors: J. LEE[1], E.-M. LEE[2], J. A. SHIN[1], ***E.-M. PARK**[2];
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Abstract: Recent studies show that shifts in energy metabolism in activated microglia are linked to their functions and immune responses in the ischemic brain. We previously reported that an antagonist of the bone morphogenetic protein, noggin, enhanced myelination in the ischemic brain during the chronic phase, and conditioned media (CM) from activated BV2 microglia treated with noggin after ischemia/reperfusion (I/R) increased the expression of myelin basic protein (MBP) in oligodendrocytes (MO3.13). To determine whether noggin induced changes in cell metabolism, metabolite profiles in BV2 and MO3.13 cells were analyzed by untargeted

metabolomics using ^{1}H nuclear magnetic resonance spectroscopy. Compared to vehicle-treated BV2 cells, noggin treatment (100 ng/mL for 3 h after I/R) suppressed the I/R-induced increase in intracellular glucose and lactate levels but increased extracellular levels of glucose and several amino acids. When MO3.13 cells were exposed to noggin CM from BV2 cells, most of the vehicle CM-induced changes in the levels of metabolites such as choline, formate, and intermediates of oxidative phosphorylation were reversed, while the glycerol level was markedly increased. An increase in glycerol level was also observed in the noggin-treated ischemic brain and was further supported by the expression of glycerol-3-phosphate dehydrogenase 1 (required for glycerol synthesis) in the cytoplasm of MBP-positive oligodendrocytes in the ischemic brains treated with noggin. These results suggest that noggin-induced changes in the metabolism of microglia provide a favorable environment for myelin synthesis in oligodendrocytes during the recovery phase after ischemic stroke.

Disclosures: **J. Lee:** None. **E. Lee:** None. **J.A. Shin:** None. **E. Park:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Title: Microglial phagocytosis of neurons protects brain during ischemic stroke

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Abstract: Ischemic stroke is responsible for a substantial number of incapacitations and fatalities worldwide. Following the onset of ischemic stroke, a robust neuroinflammatory response is triggered. Microglia, a brain-resident macrophage, can become activated and impact the development of stroke. Recent research indicated that microglia have a biphasic role in the outcome of stroke; however, the precise influence of microglia on stroke remains unclear. In this study, we elucidate the potential contribution of microglial phagocytosis in the clearance of degenerating neurons subsequent to stroke. Our findings demonstrate that the depletion of

microglia leads to an increase in the number of degenerating neurons after stroke, ultimately resulting in an increased infarct volume. Lipopolysaccharide (LPS) has been identified as an activator of microglia, promoting the engulfment of neurons both in vitro and in vivo. Furthermore, Milk-fat globule EGF factor-8 (MFG-E8) played a pivotal role in facilitating the interaction between microglia and neurons, thereby mitigating infarct volume by reducing the accumulation of dead neurons. Thus, our data strongly indicate that microglia exhibit a protective function in the context of stroke through the phagocytosis of dying neurons and alleviation of stress in the infarcted area.

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Poster

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Title: The role of epigenetic regulator, BRD4 in neuroinflammation following global cerebral ishcemia

Authors: *H. KIM[1], J. BAHN[2], R. URQUHART[1], J.-Y. HWANG[1];
[1]Dept. of Pharmacol. and Neurosciences, Creighton Univ., Omaha, NE; [2]Creighton Univ. Sch. of Med., Omaha, NE

Abstract: Global cerebral ischemia initiates cascade reactions that lead to brain damage and cognitive impairment, of which inflammation is one of the major contributors. However, molecular mechanisms by which global cerebral ischemia induces neuroinflammation, delayed and selective neuronal death in the hippocampal CA1, and cognitive impairment are not fully delineated. In this study, we performed RNA-sequencing using hippocampal CA1 tissue from early time points (24 and 48 h) after global cerebral ischemia to find the risk factors affecting neurons destined to die. Our bioinformatic analysis of the differentially expressed genes through the Ingenuity Pathway Analysis (IPA) revealed the pathways associated with immune and inflammatory response including TREM1 signaling as the top canonical pathways and a set of genes including BRD4 as the predicted transcriptional upstream regulators that can activate these canonical pathways. Because the epigenetic regulator BRD4 is highly associated with inflammatory mechanisms and TREM1 expression, among the upstream genes and canonical pathways, we focused on BRD4 and TREM1 signaling pathway to study their role in global ischemia. Using immunohistochemistry, we first examined protein expression of BRD4 in TREM1 positive cells in hippocampal CA1 region after global ischemia. The confocal images showed that BRD4 protein is expressed in the nucleus of TREM1 positive cells after global

ischemia. We further examined whether protein level of BRD4 correlates with changes in TREM1 mRNA and protein expression in hippocampal CA1 by qRT-PCR and Western blot analysis. BRD4 was significantly increased at 48 h after global ischemia, and TREM1 mRNA and protein levels were also increased at the same time point. Consistent with this, proinflammatory cytokines (NF-kB, IL-6 and IL-1β) were significantly increased in the hippocampal CA1 at 48 h after global ischemia indicating an increase in TREM1 activated neuroinflammation. TREM1 was localized in CD31 (Endothelium) and CD11b (monocytes/macrophage) positive cells, but not Iba-1 (microglia), GFAP (astrocytes) and NeuN (neurons) positive cells after global ischemia, suggesting that global ischemia increases TREM1 in infiltrating peripheral immune cells, which in turn activates neuroinflammation in hippocampal CA1 region. In addition, BRD4 inhibition by JQ1 treatment significantly attenuated global ischemia-induced neuronal death in hippocampal CA1. Taken together, these findings indicate that BRD4-dependent epigenetic regulation of neuroinflammation may be a novel therapeutic target for global cerebral ischemia.

Disclosures: H. Kim: None. **J. Bahn:** None. **R. Urquhart:** None. **J. Hwang:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Title: Rapid complement activation induced by acute hyperglycemia worsens blood-brain barrier leakage and ischemic stroke outcome

Authors: *H. CHEN[1], T. CHIANG[2], R. KOPCHOCK, III[1], A. KIM[3], S. TOMLINSON[7], T. BLISS[4], M. Y. CHENG[5], G. K. STEINBERG[6];
[1]Neurosurg., Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Stanford, CA; [3]Neurosurg., Stanford Univ., Redwood City, CA; [4]Dept of Neurosurg, Stanford Univ., STANFORD, CA; [5]Neurosurg., Stanford Univ., Stanford, CA; [6]Stanford Univ., STANFORD, CA; [7]Med. Univ. of South Carolina, Charleston, SC

Abstract: Background: Acute hyperglycemia, which occurs in over 40% of ischemic stroke patients, regardless of pre-existing diabetes, worsens stroke outcome. Understanding the mechanisms of hyperglycemia-exacerbated stroke injury is vital for developing novel treatments. Here we investigate the role of complement activation in hyperglycemic-exacerbated damage in rodent stroke. **Method:** Male C57/BL6 mice (10-11 weeks) were subjected to 30 min suture induced-middle cerebral artery occlusion, followed by suture removal to mimic thrombectomy-

induced recanalization in clinical stroke. Acute hyperglycemia was induced by glucose injection 10 min before stroke. Mice were sacrificed at 4.5 and 24 hr post-stroke to analyze brain swelling, blood-brain barrier (BBB) leakage and hemorrhagic transformation (HT); or survived to 14 days to examine mortality rate, neurological deficit and motor-sensory functions. Complement activation was evaluated by immunostaining for the activation product C3d. To investigate the significance of C3 activation in hyperglycemic-exacerbation of stroke pathology, we utilized C3 knock-out mice or pharmacological inhibition of C3 activation using targeted complement inhibitor CR2-Crry fusion protein (injected intraperitoneally 30 min after reperfusion). **Result:** Hyperglycemia rapidly worsens stroke outcomes as evidenced by increased BBB leakage ($p<0.0001$), brain swelling ($p<0.05$), and HT ($p<0.0001$) at 4.5 hr after stroke, compared to normoglycemia. Hyperglycemic stroke mice also exhibit higher mortality (100% vs 25%, $p=0.0008$), body weight loss, and impaired behavioral performance at the sub-acute phase. Notably, acute hyperglycemia rapidly increased plasma complement C3 levels at 1 and 2 hr after stroke ($p<0.01$), accompanied by rapid and time-dependent activation of C3 in ischemic brain vessels as indicated by increased vascular C3d; C3d levels positively correlated with brain swelling and HT ($p<0.01$). Vascular C3d was markedly reduced in the absence of reperfusion. Blocking complement activation either using C3 knock-out mice or pharmacologically, by injecting the C3 inhibitor CR2-Crry after reperfusion, significantly reduced the detrimental effects of hyperglycemia. **Conclusion:** Rapid vascular activation of complement C3 is a significant driver of hyperglycemic-exacerbated pathology in experimental stroke. Inhibiting C3 activation could be a potential therapeutic approach to improve hyperglycemic stroke outcome. The role of systemic C3 in other pathologies with increased BBB leakage such as aging, should be explored.

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Poster

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Title: Synaptic Zn^{2+} accumulation and non-canonical Ca^{2+} channel activity in vulnerable brain: an unconventional mechanism of spreading depolarization related injury

Authors: *M. BENNETT[1], J. WEISEND[1], R. A. MORTON[1], A. P. CARLSON[2], C. W. SHUTTLEWORTH[1];

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Abstract: Introduction: Spreading depolarizations (SDs) are strongly linked to injury progression in energy-depleted brain tissue. We have previously shown that L-type voltage-gated Ca^{2+} channels (VGCC) and synaptic Zn^{2+} accumulation contribute to initiation and propagation of SD in brain slices. In the current study we tested contributions of Zn^{2+} and L-type VGCCs to detrimental consequence of SD in metabolically depleted tissue. **Method:** SD was induced in coronal brain slices from mice, by focal microinjection of KCl in a previously-described model of metabolic depletion (Exp Neurol 305 (2018) 121-128). SD was monitored using intrinsic optical signals (IOS), extracellular recordings, and fluorescence imaging used to monitor both extracellular Zn^{2+} accumulation and (FluoZin-3) and neuronal Ca^{2+} (GCamP6s). **Results:** As previously reported, reduction in metabolic substrate availability impaired recovery after SD (-24.8% decrease in IOS signals and 51.8% fEPSP recovery, post-SD, n=5-6). Nimodipine pre-exposure (10μM) prevented deleterious effects of SD (0.25% IOS increase and 77.4% fEPSP recovery; n=7-10). GCamP6s imaging did not reveal a detectable decrease in Ca^{2+} accumulation following nimodipine blockade (n=5), raising the possibility of a non-Ca^{2+} dependent VGCC mechanism of neuronal impairment. ZX1 (100μM) chelation improved tissue recovery (0.55% IOS increase and 95.3% fEPSP recovery; n=6). Tissues from ZnT3 knockout animals showed similar protection (22.1% IOS increase and 93.1% fEPSP recovery; n=5-6). FluoZin-3 imaging was consistent with a synaptic source of Zn^{2+} in effects described above. **Conclusions:** These results are consistent with synaptic Zn^{2+} release and accumulation via L-type VGCCs contributing to excessive ionic burden and impaired recovery from SD events. Selective pharmacological targeting of synaptic Zn^{2+} accumulation may be a useful adjunct approach to target deleterious consequences of SD in ischemic brain.

Disclosures: M. Bennett: None. **J. Weisend:** None. **R.A. Morton:** None. **A.P. Carlson:** None. **C.W. Shuttleworth:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.15/V10

Topic: C.08. Ischemia

Support: NS106901
GM109089

Title: Spreading Depolarization modifies genes expression levels differently between the stroke core and the penumbra.

Authors: *M. DELL'ORCO[1], M. C. BENNETT[1], L. LI[1], J. E. WEISEND[1], N. I. PERRONE-BIZZOZERO[1], L. CUNNINGHAM[1], A. P. CARLSON[2], C. W. SHUTTLEWORTH[1]; [2]Neurosurg., [1]Univ. of New Mexico, Albuquerque, NM

Abstract: Spreading depolarization (SD) occurs in stroke brain and are strongly linked to infarct enlargement. SDs usually originate near ischemic foci and propagating relatively widely throughout peri-infarct and surrounding tissues. Our previous studies in uninjured brain have shown SD-induced changes in expression levels of genes known to regulate synaptic plasticity and neurogenesis. The aim of the current study was to analyse SD influences on gene expression changes in stroke core and penumbra. SDs were induced repetitively with focal KCl application (4 SDs at 30 min intervals) in a distal middle cerebral artery stroke model (dMCAO) in C57Bl/6 mice. Two hours after onset of the initial SD, cortical slices were collected and RNA was extracted 1) from either total hemisphere (to compare ipsilateral and contralateral), or 2) from 2 different regions of the ipsilateral hemisphere: stroke core and stroke penumbra. Total RNA was subjected to either RNA-seq or spatial genomics to identified differentially expressed genes (DEGs). In the stroke core, compared to the contralateral cortex, top DEGs include genes encoding the neurotrophic factor BDNF, intermediate early genes FOS, and NPAS4, previously associated with ischemic preconditioning. We also found significantly increased levels of other cell proliferation related genes including DUSP6, plasticity related gene ARC, and inflammation related genes as PTGS2, EGR2 and NR4A1. When comparing the penumbral area with the core, we found differential expression of genes related to synaptic activity rather than proliferation, including SCN4, DRD2, ADORA2A and CamKIIb. Finally, when we compared the penumbra with contralateral tissue, we found increased levels of plasticity and proliferation associated genes (BDNF, NPAS4, ARC, FOS, EGR1, and PTGS2) and decreased levels of neuronal activity related genes (SCN4, ADORA2A, and DRD2). These results suggest that SDs regulate gene expression changes inducing activation of long-term repair process in the stroke penumbra, while short-term survival pathways are preferentially activated in core regions. This study identified novel targets that could be used to test to hypotheses of SD involvement in plasticity or recovery in surviving peri-infarct tissue.

Disclosures: M. Dell'Orco: None. **M.C. Bennett:** None. **L. Li:** None. **J.E. Weisend:** None. **N.I. Perrone-Bizzozero:** None. **L. Cunningham:** None. **A.P. Carlson:** None. **C.W. Shuttleworth:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

Location: WCC Halls A-C

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Topic: C.08. Ischemia

Support: Boag Family Endowment in Neuroscience
R. S. McLaughlin Fellowship
Ontario Graduate Scholarship

New Frontiers in Research Fund
Heart & Stroke Foundation of Canada

Title: Investigating the Mechanism and Identity of an Activator of Spreading Depolarization

Authors: *J. A. HELLAS[1], P. J. GAGOLEWICZ[2], C. A. LOWRY[1], D. ANDREW[3];
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Abstract: Stroke leads to irreversible ischemic brain injury and is the second leading cause of death globally, with incidence rising each year [1]. The brain is highly metabolically demanding and requires a steady blood flow containing sufficient oxygen and glucose for normal function. During stroke, traumatic brain injury (TBI), or sudden cardiac arrest (SCA), cerebral blood flow is halted locally, with reduced flow in collateral regions [2]. With a lack of oxygen and glucose, neurons cannot generate adenosine triphosphate (ATP), causing rapid failure of ATP-dependent cellular pumps and thus loss of neuronal function within minutes [3]. The sodium-potassium transporter fuelled by ATP (Na^+/K^+ pump) fails within minutes of stroke onset, and quickly promotes spreading depolarization (SD). SD is a propagating wave of inactivation traversing the higher brain grey matter. SD can recur over hours or days, thereby expanding the ischemic core [4-8]. The resulting neuronal injury caused by SD can leave patients with permanent neurological deficits, yet there are no pharmacological treatments [4, 6, 7, 9]. Fundamentally, we do not understand the molecular events driving either the spread *or* the depolarization.
At picomolar concentrations, a marine poison palytoxin (PLTX) converts the Na^+/K^+ transporter into an open Na^+/K^+ channel, thereby inducing SD in brain slices, as well as prehemolytic swelling and then hemolysis of red blood cells. Here, we developed a bioassay for a proposed endogenous SD activator (SDa) that we suspect is released by stressed grey matter to initiate and drive SD in a PLTX-like manner. We first captured an SDa sample by exposing ~30 rodent brain slices to oxygen and glucose deprived (OGD) artificial cerebrospinal fluid (aCSF), removed the slices, and replaced O_2 and glucose. This 'Post-SD aCSF' evoked SD in naïve slices with 78-82% frequency. 'Pre-SD aCSF' from slices not exposed to OGD had no such activity. We then ruled out that pH changes, released K^+, or glutamate were responsible. Finally, we built upon previous work from the Andrew lab where trace amounts of PLTX seemed to 'prime' the Na^+/K^+ pump for opening, facilitating hemolysis. We found that this priming phenomenon could be replicated in tissue slices.
The isolated Post-SD aCSF should serve as a reasonably purified SDa solution, given the absence of cellular disruption/extraction procedures. A stronger understanding of the activity and identity of an endogenous SDa and an improved understanding of the molecular mechanisms driving SD will help elucidate novel targets for reducing or stopping recurrent SDs in clinical populations suffering stroke, TBI or SCA.

Disclosures: **J.A. Hellas:** None. **P.J. Gagolewicz:** None. **C.A. Lowry:** None. **D. Andrew:** None.

Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Program #/Poster #: PSTR265.17/V13

Topic: C.08. Ischemia

Support: NIH Grant R01MH086638

Title: Multiscale modeling of ischemia and spreading depolarization

Authors: *A. J. H. NEWTON[1], C. KELLEY[2,4], S. GUO[5], J. WANG[5], S. ZINK[6], M. M. DISTASIO[7], R. A. MCDOUGAL[8,9,10], W. W. LYTTON[3,11,12];
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Abstract: Spreading depolarization (SD) is a neuronal phenomenon characterized by the propagation of a depolarization wave at a rate of approximately 2-7 mm per minute, accompanied by ion homeostasis disruption and subsequent minutes-long neuronal silence/depression. SD is observed in neurological disorders like migraine aura, traumatic brain injury, and ischemic stroke, where it worsens the energy crisis by increasing ATP and oxygen demand in affected tissue. The interplay between SD and ischemia can contribute to secondary brain injury. Blood vessels play a contributing role in SD by as a source of oxygen and nutrient supply to the affected tissue. Understanding these mechanisms is important for targeted interventions in conditions like ischemic stroke.

We developed NEURON/NetPyNE simulator models to investigate ion homeostasis at subcellular and tissue scales. At the subcellular scale, we optimized a CA1 pyramidal neuron model to maintain ion homeostasis under physiological conditions. Under ischemic conditions our model predicted greater calcium accumulation in basal dendrites, making them more vulnerable to excitotoxicity. In contrast, the distal-apical dendrites suffered more chloride influx, a contributor to dendritic beading.

At the tissue scale we used an established cortical microcircuit model; equipping neurons with additional homeostatic mechanisms (Na^+/K^+-ATPase, KCC1, NKCC2) and adding energy-dependent clearance of extracellular K^+ by glia. We used RxD to track the intracellular and extracellular concentration dynamics of Na^+, K^+, Cl^- and O_2. Histologic images of a 2.0 x 2.3cm cross-section of the human cortical plate in V1 with immunostaining for CD34, determined the locations of 918 capillaries (mean capillary density: 199.6/cm^2; mean±SD capillary cross-sectional area: 16.7±11.9μm^2). These loci provided the sources of oxygen for our in vivo model. SD was reliability triggered in this in vivo network model by a bolus of K^+ in layer 4. Neuronal Depolarization occurred in all cortical layers, with pathological activity spreading both through

connectivity and extracellular diffusion. Neuronal proximity to an oxygen source was a good predictor of its ability to maintain physiological firing rates.

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Poster

PSTR265. Ischemia: Neuroinflammation and Spreading Depolarization

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Program #/Poster #: PSTR265.18/V14

Topic:

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Mr. Paul Slavik
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NYU School of Medicine

Title: Molecular heterogeneity of ischemic injury-induced reactive astrocytes.

Authors: *R. D. KIM[1], A. E. MARCHILDON[1], P. HASEL[1], P. W. FRAZEL[1], A. X. GUO[1], S. A. LIDDELOW[1,2,3];
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Abstract: Astrocytes undergo robust gene expression changes in response to a variety of perturbations such as infection, disease, and acute insults, including ischemic injury. How these transitions are affected by time and sex, as well as how heterogeneous and spatially distinct various reactive astrocyte populations are, remain unclear.
To better understand the molecular and temporal diversity of various astrocyte populations in response to injury, we performed spatial transcriptomics and single nucleus RNAseq of ~138,000 forebrain astrocytes isolated from Aldh1l1-EGFP/Rpl10a mice at 1, 3, and 14 days after ischemic injury induced by Rose Bengal photothrombosis.
We found that injury induces a widespread and temporally diverse response across many astrocyte subtypes. We also identified clusters unique to injury-induced reactive astrocytes, including interferon-responsive reactive astrocytes (IRRAs) that are rapidly induced at 1 day and persist up to 14 days post-injury; this population, in addition to expressing many interferon response genes (e.g. *Igtp, Iigp1, Ifit3,* etc.), appears to be Infar1-dependent. Another unique injury-induced reactive astrocyte cluster expresses proliferative markers (e.g. *Mki67, Top2a, Pola1,* etc.) only at 3 days post-injury. Spatial transcriptomics and *in situ* cluster validation indicated that these lowly abundant reactive astrocyte populations (0.6% and 0.4% for interferon-

responsive and proliferative reactive astrocytes, respectively) are spatially restricted to locations that are likely functionally important in the stabilization and resolution stages following injury. This work highlights the utility of combining multiple profiling modalities, as well as the importance of properly powering the study of rare but potentially biologically meaningful reactive astrocyte populations. Together, these datasets provide a powerful resource for probing injury-induced reactive astrocyte heterogeneity and can be used to guide functional interrogation of biologically meaningful reactive astrocyte substates to understand their pro- and anti-reparative functions following acute injuries such as stroke.

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Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.01/V15

Topic: C.09.Stroke

Support: RF1NS127413

Title: Trpm2 channel deletion in neurons reduces injury following ischemic stroke and improves post-stroke cognitive function

Authors: ***K. A. COAKLEY**[1], J. E. ORFILA[2], C. M. ANDERSON[2], A. M. LOEHFELM[2], V. P. WRIGHT[2], P. K. WAITS[2], P. S. HERSON[3];
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Abstract: Background: Emerging evidence implicates post-stroke cognitive impairment as a major contributor to long-term disability. Therefore, optimal therapeutic targets reduce acute ischemic injury and enhance post-stroke brain function. Strong data demonstrates that a novel TRPM2 channel antagonist (tat-M2NX) provides neuroprotection and improves synaptic function, thereby reducing post-stroke cognitive impairment (PSCI). Hypothesis: Knockout of neuron-specific TRPM2 channel expression reduces infarct volume and enhances functional recovery following MCAO Methods: Transient MCAO (60 min) was performed on adult (8-10 week) male and female TRPM2 neuron-specific KO (TRPM2fl/fl, CaMKII Cre) and TRPM2 floxed controls (TRPM2fl/fl). Hemispheric infarct volume analyzed from MRI (T2) images 3 days and 30 days post-injury by a blinded investigator. Extracellular field recordings of CA1 neurons were performed in acute hippocampal slices prepared both 7 days and 30 days after recovery from MCAO to analyze synaptic plasticity (LTP). Results: We observed that neuronal-specific TRPM2 channel knockout reduces acute ischemic injury (infarct volume) in male

animals, while having minimal effect on female mice. Consistent with the hypothesis that neuronal TRPM2 channels contribute to ischemia-induced synaptic dysfunction, recordings obtained in brain slices from neuronal TRPM2 channel KO mice (TRPM2fl/fl-CaMKII CRE) mice 7 days after recovery from 60 min MCAo exhibited intact hippocampal plasticity compared to control TRPM2fl/fl mice not expressing CRE. Male sham control mice exhibit robust LTP of 163±10.4% (n=3) compared to 115±5.6% (n=4) in TRPM2fl/fl mice after MCAO. Neuronal KO exhibited 175±9.8% (n=2). Similarly, female mice had control LTP of 170±6.8% (n=4) compared to 125±6.8% (n=3) in TRPM2fl/fl mice after MCAO. Neuronal KO exhibited 208±7.8% (n=5, $p<0.05$ ANOVA compared to TRPM2fl/fl MCAO). Conclusion: Our data highlight that TRPM2 channels expressed in neurons contribute to both acute injury following transient ischemic stroke and subacute/chronic functional recovery.

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Poster

PSTR266. Stroke: Models and Mechanisms

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Program #/Poster #: PSTR266.02/V16

Topic: C.09.Stroke

Support: NINDS K08 NS083740
NINDS RF1 NS114336

Title: Spon1 as a candidate driving oligodendrocyte remyelination in white matter stroke

Authors: *V. LUBERA, Y. KOMURO, E. FONT BELMONTE, J. D. HINMAN;
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Abstract: Stroke is a leading cause of long-term disability and is the second most common cause of death worldwide. Small vessel ischemic strokes account for 25% of all strokes and occur silently in the brain with a far higher incidence. Ischemic injury to brain white matter preferentially damages myelin-forming oligodendrocytes. The identification of molecular targets in mature myelinating oligodendrocytes that can promote remyelination after stroke are needed to minimize stroke's devastating impact on the brain and drive neurological recovery. White matter ischemic injury is recognized to enhance oligodendrogenesis, whereby stroke-responsive oligodendrocyte progenitor cells migrate to the lesion and differentiate into mature myelinating oligodendrocytes. This OPC-oligo differentiation after stroke is severely limited and shunts cells to a predominant astrocyte fate. However, the self-repair mechanism of injured but surviving oligodendrocytes in the peri-infarct area of stroke remains poorly understood. To identify molecular pathways that can promote remyelination in mature stroke-injured oligodendrocytes, we used TRAP-seq from CNP-Rpl10a-EGFP transgenic mice (*n*=5/grp) at 3 days following the induction of subcortical ischemic stroke vs. sham. Stereotaxic induction of stroke in the

subcortical white matter using N(5)-(1-Iminoethyl)-L-Ornithine HCl (L-NIO) produces a focal white matter stroke in 3-4 month old male mice. After 3 days post-stroke, white matter tissue directly underneath the left sensorimotor cortex was dissected. TRAP-seq from EGFP+ mature oligodendrocytes results in enrichment of mature oligodendrocyte marker genes and isolates the mature oligodendrocyte transcriptome after stroke. Gene ontology analysis demonstrates enrichment for cell-cell adhesion pathways and among the top differentially regulated genes in stroke-injured oligodendrocytes is the transmembrane cell adhesion molecule, Spon1. Spon1 is essential for neural growth and cell adhesion, and its overexpression in a mouse model of Alzheimer's disease leads to cognitive improvements. Using TRAP-qPCR and in situ RNA detection, we show that Spon1 is progressively up-regulated by oligodendrocytes at 1, 3, and 7 days after stroke. Gain of function expression of Spon1 in stroke-injured white matter results in improved remyelination after stroke and stimulates both mature oligodendrocytes to remyelinate but also promotes post-stroke axonogenesis as well as OPC differentiation. The findings suggest Spon1 is a critical cell adhesion molecule temporally regulated by mature oligodendrocytes after stroke and can trigger post-stroke remyelination.

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Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.03

Topic: C.09.Stroke

Title: Visualization of post-stroke glial environment and collateral axonal sprouting in the adult mouse central nervous system

Authors: *I. N. SYED[1], M. KENWOOD[2], K. POINSATTE[4], D. BETZ[5], P. CHERIAN[6], D. RAMIREZ[4], M. P. GOLDBERG[3];
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Abstract: Stroke is the leading cause of disability in the United States. Following stroke, the central nervous system experiences various forms of plasticity. One form of this plasticity is the innervation of axon collaterals from the contralesional motor region of the brain and uninjured corticospinal tract (CST). Prior studies have found early reactive gliosis in the distal end of the injured CST. However, the time course of reactivity of glial cells and their role in facilitating plasticity after stroke remain largely unknown. We used immunofluorescence assays and AAV injections to measure the time course of glial activation and label the emergence of axonal sprouting in the distal spinal cord and contralesional motor cortex, respectively. Additionally, we

established a data analysis pipeline to visualize and quantify results obtained from confocal microscopy and serial two-photon tomography (TissueCyte). We show growth cones in typical motor neuron innervating regions and reactive gliosis in the uninjured CST across various time points after unilateral photothrombotic stroke. Visualizing growth cones in vivo may allow for further study into the mechanisms of collateral axonal sprouting from the uninjured CST of the adult CNS. Further, our results help to understand the role of the glial environment during stroke recovery.

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Poster

PSTR266. Stroke: Models and Mechanisms

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Program #/Poster #: PSTR266.04/V17

Topic: C.09.Stroke

Title: Corticospinal neurons form monosynaptic connections to ipsilesional spinal cord alpha motor neurons following focal cortical strokes in mice

Authors: *M. KENWOOD[1], K. POINSATTE[3], A. AJAY[3], A. NAWABY[3], W. XU[3], D. BETZ[2], E. J. PLAUTZ[3], D. M. RAMIREZ[3], M. P. GOLDBERG[2];
[1]Neurol., [2]Univ. of Texas Hlth. Sci. Center, San Antonio, San Antonio, TX; [3]UT Southwestern Med. Ctr., Dallas, TX

Abstract: Stroke leaves many patients with significant motor impairment. Sprouting of the contralesional corticospinal tract (cCST), into the injured spinal hemicord is associated with improved motor recovery after unilateral primary motor cortex stroke. In adult mice, most corticospinal neurons project to spinal interneurons, and few synapse directly on alpha motor neurons. We examined the distribution of newly formed corticospinal synapses in the mouse spinal cord, using genetically encoded tracers, 3D microscopy, and a spinal atlas with machine learning-based automated classification and registration. We tested the hypothesis that subsets of cCST neurons form direct connections with AMNs in the injured hemicord after unilateral motor cortex stroke in adult mice. We induced a photothrombotic motor cortex stroke or performed sham surgery (n=4 per group) in 8-11 week old male C57/B6 mice and administered a contralesional motor cortex injection of an anterograde adeno-associated virus expressing both membrane-targeted tdTomato and synaptically-targeted eGFP. Cervical spinal cords were subjected to volumetric imaging via serial two-photon tomography (TissueCyte 1000) to characterize synaptic and axonal density of cCST collaterals in whole cervical spinal cords in both stroke and sham mice. Unbiased, global quantification of axonal and synaptic density across the entire cervical cord was accomplished by the development of a custom automated image analysis pipeline, incorporating a novel 3D spinal cord reference volume, published spinal cord annotations comprising 47 distinct anatomical regions (SpinalJ), and machine learning based

pixel classification. We observed cCST synapses in the 6-week post-stroke ipsilesional hemicord, with direct connections to alpha motor neurons controlling the levator scapula, phrenic muscles, supraspinatus & infraspinatus, trapezius & sternomastoid, infrahyoid, biceps, deltoid, and forearm extensor (Log2 FC > 4). Formation of new direct connections from uninjured contralesional primary motor cortex to alpha motor neurons may contribute to recovery of motor function after stroke.

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Poster

PSTR266. Stroke: Models and Mechanisms

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Program #/Poster #: PSTR266.05/V18

Topic: C.08. Ischemia

Support: NIH Grant 5T32GM007200-48

Title: Spatiotemporal characterization of unilateral electrophysiological depression in two pediatric patients

Authors: ***M. LOE**[1,3], A. L. SCHWAMB[3], J. WAGNER[3], R. LANDRE[4], M. MORRISSEY[4], S. R. TOMKO[2], R. M. GUERRIERO[2], S. CHING[3];
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Abstract: EEG monitoring is used to detect changes in brain electrical activity of pediatric patients with a variety of conditions, including acute ischemic, traumatic, or metabolic injury to the brain. In this retrospective analysis, two pediatric patients without a history of stroke or cerebrovascular disease presented to the ICU with new-onset stroke symptoms, without magnetic resonance imaging (MRI) evidence of stroke. Despite this, both patients demonstrated unilateral changes in EEG power contralateral to their stroke symptoms. Patients received standard clinical care, as well as continuous EEG monitoring. Both patients' stroke symptoms resolved and EEG activity normalized over the course of days. Subsequently, both patients developed stroke symptoms corresponding to the contralateral hemisphere. Again, EEG monitoring demonstrated similar changes in EEG power in the contralateral hemisphere to symptoms. Each patient had over 72 hours of EEG data, non-contrast brain MRI, and brain MR angiography. Additional quantitative EEG analysis was conducted to describe the spatial propagation of electrophysiological changes observed in acute, alternating hemiparesis during EEG monitoring. We quantified the alternating asymmetry using analytical tools previously developed by our group to characterize the rate and spatial orientation of these unilateral depressions and subsequent recovery. These unilateral depressions correlated with known hemodynamical

changes confirmed on cerebral angiography; these cerebrovascular changes are posited to drive the abnormal brain electrical activity. The unilateral depression found may be an exaggerated correlate of cortical spreading depressions (CSDs), which are hypothesized to be the electrophysiological consequence of cerebrovascular changes in strokes and migraines. While this case study is limited by size and the availability of data retroactively, it provides useful insight into the mechanisms by which we might refine methods for the detection of similar cerebrovascular insults in the future.

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Poster

PSTR266. Stroke: Models and Mechanisms

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Program #/Poster #: PSTR266.06/V19

Topic: C.08. Ischemia

Title: Psilocybin improves motor outcomes following photothrombotic stroke and increases peri-infarct plasticity

Authors: *H. STRONG[1], R. M. HINES[2], D. J. HINES[2];
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Abstract: Narrow time windows of intervention after stroke onset limit recovery and contribute largely to long term disability. Endogenous mechanisms of recovery contribute to restricting boundaries of damaged tissue and regulating cell death and survival. Glial cells modulate tissue survival and successful formation of synaptic connections regulating peri-infarct plasticity. Identifying therapeutics capable of enhancing recovery of damaged tissue through increasing or strengthening synaptic connections of peri-infarct tissue would widen the time window of treatment. Persistent synaptic plasticity enabled by psilocybin indicates its potential for therapeutic use to enhance endogenous mechanisms of recovery after stroke. The capacity of psilocybin to incite plasticity synergistic with endogenous peri-infarct recovery after stroke remains unknown. In this study, we examine the ability of psilocybin to alter stroke recovery by comparing peri-infarct plasticity and behavioral sparing after photothrombotic motor cortex stroke. Administering psilocybin after stroke led to increased dendritic arborization and spine density in peri-infarct tissue along with glial cell morphology changes. To identify if dendritic recovery was accompanied by behavioral sparing we tested motor outcomes using ladder rung walking and saw improved performance when psilocybin was administered after photothrombosis. These results show psilocybin improves post-stroke motor recovery through increasing dendritic plasticity without exacerbating endogenous recovery mechanisms. Enhancing endogenous mechanisms of peri-infarct recovery through psychedelics provides evidence of a synergistic relationship between glial cells and psychedelics after stroke. Ongoing

work examining the mechanisms of psilocybin plasticity in relation to glial cells after stroke provides novel therapeutics and understanding of the mechanisms that necessitate recovery.

Disclosures: H. Strong: None. **R.M. Hines:** None. **D.J. Hines:** None.

Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.07/V20

Topic: C.08. Ischemia

Support: NIH Grant NS090904
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Title: Activated protein C analog protects ischemic brain injury in mice via β-arrestin-2-dependent signaling

Authors: *B. XIANG[1], Y. WANG[1], M. ZHANG[1], J. A. FERNÁNDEZ[2], J. H. GRIFFIN[2], B. V. ZLOKOVIC[1];
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Abstract: 3K3A-APC is a recombinant analog of activated protein C (APC) which is an endogenous protease with multiple functions in the body. Compared to APC, 3K3A-APC has reduced anticoagulant activity but preserved cell signaling activities. In the brain, 3K3A-APC exerts neuroprotective effects after an acute or chronic injury. 3K3A-APC is currently under clinical assessment (Phase 3) as a neuroprotective agent following acute ischemic stroke. β-arrestin-2 is expressed in many types of cells and plays important roles in various physiological processes. We hypothesized that β-arrestin-2 is required for the blood-brain barrier (BBB) integrity and neuroprotection after stroke. Using a transient proximal middle cerebral artery occlusion (tMCAO) stroke model, we studied whether the neuroprotection effect of 3K3A-APC depends on β-arrestin-2. Our data show that murine 3K3A-APC (0.8 mg/kg), administered intraperitoneally 10 min and 4 h after tMCAO in wild-type mice compared to vehicle, reduced infarct and edema volume and motor neurological score by 55-61%. Similar reductions in BBB breakdown and number of degenerating neurons were observed. The effects of 3K3A-APC on neuroprotection and blood-brain barrier protection were lost in β-arrestin-2 null mice. Thus, our data supports that 3K3A-APC reduces ischemic brain injury via β-arrestin-2-dependent signaling pathways.

Disclosures: B. Xiang: None. **Y. Wang:** None. **M. Zhang:** None. **J.A. Fernández:** None. **J.H. Griffin:** None. **B.V. Zlokovic:** None.

Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.08/V21

Topic: C.08. Ischemia

Support: Italian Ministry of Health (Ricerca Corrente 2021-2022) to IRCCS Mondino Foundation, Pavia, Italy.
#NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006). (DN.1553 11.10.2022)

Title: Investigating the impact of novel personalized neurostimulation strategies to promote recovery after an ischemic lesion in anesthetized rats

Authors: *M. CARÈ[1], F. BARBAN[1], R. GRECO[2], M. DI FLORIO[1], D. J. GUGGENMOS[3], C. TASSORELLI[2], M. CHIAPPALONE[1];
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Abstract: Stroke is a major global cause of death and disability, but current therapies are limited as standard post-stroke rehabilitation with physical therapy rarely leads to full restitution of function. This is in part due to impaired communication between unaffected brain areas following the lesion. New techniques, especially those using tailored stimulation patterns that match the dynamics of brain networks have shown promise in promoting plasticity and motor recovery. However, clinical stimulation-based therapies rely on standardized protocols, which may explain inconsistent outcomes. Creating personalized stimulation protocols based on the intrinsic activity may significantly improve efficacy of these approaches. The purpose of this study was to advance neurostimulation techniques by customizing electrical stimulation based on individual electrophysiological features. Our main goals were: to examine the neurophysiological outcomes of an ischemic lesion and to design and characterize short-term effects of novel personalized neurostimulation techniques in an animal model of stroke. We implanted Long Evans male rats with MEAs (microelectrode arrays) in the rostral forelimb area (RFA) and Somatosensory cortex (S1) following ischemic lesion induction in the caudal forelimb area (CFA) using local Endothelin-1 injections. We evaluated the immediate impact of the lesion and tested personalized stimulation protocols using an open-loop paradigm on anesthetized rats. Personalization involved designing stimulation patterns to replicate the intrinsic dynamics in the target area. Three methods were employed: 1) Exponential Stimulation, which created a new spike sequence based on an exponential distribution with mean value equal to the average firing rate of the target brain area; 2) Repeated Stimulation, which generated a stimulation pattern by replaying and repeating recorded spontaneous activity; 3) Shuffled Stimulation, which generated a new spike sequence based on inter-spike intervals (ISI) using data acquired from the experimental network. We found that the lesion significantly reduced spontaneous firing activity in S1 and RFA. The repeated stimulation protocol notably increased spiking activity, consistent with the effects of Activity-Dependent Stimulation, a closed-loop

paradigm known to promote post-lesion recovery. Non-periodic, tailored stimulation is a promising avenue for restoring firing patterns in the damaged brain. These findings have significant implications for advancing therapeutic strategies for neurological diseases and facilitating the translation of personalized electroceutical to clinical practice.

Disclosures: **M. Carè:** None. **F. Barban:** None. **R. Greco:** None. **M. Di Florio:** None. **D.J. Guggenmos:** None. **C. Tassorelli:** None. **M. Chiappalone:** None.

Poster

PSTR266. Stroke: Models and Mechanisms

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Topic: C.08. Ischemia

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Title: Polyunsaturated fatty acid (PUFA)-enriched diet mitigates secondary sequelae following VCID-associated cerebral hypoxia

Authors: *J. TOMBERLIN[1,2], J. KURTZ[2], J. EDWARDS[2], E. KARAKAYA[2], S. BEYAZ[3], A. ERGUL[2], O. ALBAYRAM[2,1];
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Abstract: Vascular contributions to cognitive impairment and dementia (VCID), an umbrella term encompassing multiple vascular disorders, is the second leading cause of dementia behind Alzheimer's disease and related dementia (ADRD). Additionally, VCID and ADRD have overlapping risk factors, which can be managed by improving cardiovascular health. Compelling evidence supports that diets rich in polyunsaturated fatty acids (PUFAs) derived from fish oil (FO) can reduce ADRD-associated cognitive decline, potentially through lowered neuroinflammation and reduced white matter (WM) degeneration. However, how long-term PUFA enrichment affects WM integrity, fatty acid metabolism and trophic response in a model of VCID-associated cerebral hypoperfusion has not been assessed. In our model, C57/BL6 male mice were given either a purified control diet (Control Diet) or novel 2% FO-supplemented diet (2%-FO-Supp Diet) for 3 months (3M) prior to either a sham or bilateral carotid artery stenosis (BCAS) surgery model of VCID. Purified or 2%-FO-Supp Diet was continued for up to 6M post-

injury and body weight and food consumption were monitored on a weekly basis. Mice were subjected to a neurobehavioral battery at baseline and 1, 3, & 5M post-injury alongside cerebral blood flow assessment at 5 days, 1, 3, & 5M via laser doppler flowtometry. Finally, mice were euthanized and tissue samples from the carotid arteries, brain, and heart were collected 6M post-injury. Preliminary results indicate that 2%-FO-Supp Diet BCAS mice maintained a significantly healthier weight following injury compared to control BCAS mice. All BCAS mice also had observable cognitive decline and lowered cerebral blood flow (CBF) starting at 3M post-injury that worsened over time compared to controls. Additionally, 2%-FO-Supp Diet BCAS mice potentially had slowed cognitive decline compared to control diet BCAS mice at both 3M and 5M assessed via Barnes Maze and Morris Water Maze respectively. Notably, we observed that 2%-FO-Supp Diet-BCAS mice have improved trophic function, white matter integrity, and increased free fatty acid signaling response compared to Control Diet BCAS mice. Further, analysis pending, we anticipate that 2%-FO-Supp Diet-BCAS mice will have lowered brain hypoxia and neuroinflammation compared to Purified Diet-BCAS mice. Successful completion of these translational studies will provide novel insights into the long-term vaso-neuronal protective effects of PUFAs in VCID.

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Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.10/V23

Topic: C.08. Ischemia

Support: NASA 80NSSC22M0027

Title: Hemoglobin mRNA is diminished in the caudate nucleus with chronic hydrocephalus

Authors: G. IVEY, E. BARRETT, M. HART, *J. W. SHIM;
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Abstract: The expression of hemoglobin genes, such as the alpha and beta globin genes, is tightly regulated, and once hemoglobin gene expression is reduced in the brain, it is likely that cerebral hemoglobin protein is also decreased. However, that is not always the case for less tightly regulated molecules such as haptoglobin, CD163, and vascular endothelial growth factor (VEGF). We have conducted whole transcriptome RNA-sequencing (RNA-seq.) using human postmortem brains at age >65 years with chronic hydrocephalus (CH) and found that genes encoding globin proteins are ranked in the top 5 among roughly 2,000 differentially regulated candidates sorted by effect size and statistical significance. Specifically, genes encoding haptoglobin (HP; top 1 of 2,144) and hemoglobin (HBA2; top 2 and HBA1; top 4 of 2,144) are significantly diminished ($P<0.0001$) while VEGF-A (top 1955 of 2144) gene expression is

elevated (P=0.04) in the caudate nucleus with CH as compared to age-matched controls. These results suggest that haptoglobin and hemoglobin may play a role in the development of hydrocephalus, and their decreased levels may contribute to the progression of this condition. VEGF-A may also play a role in hydrocephalus, as it can increase the permeability of blood vessels and lead to an increase in the volume of cerebrospinal fluid (CSF).

Disclosures: G. Ivey: None. **E. Barrett:** None. **M. Hart:** None. **J.W. Shim:** None.

Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.11/V24

Topic: C.08. Ischemia

Title: Lactic acidemia as a predictor and prognosticater of vasospasm in Subarachnoid Hemorrhage

Authors: *D. LAL;
Neurosurg., Natl. Hosp. Kandy, Kandy, Sri Lanka

Abstract: Background: Lactic acidemia is a known sequale of organ ischemia and indicates the severity and prognosis. It’s not rare to see lactic acidemia with or without acidosis in ischemic conditions of the brain.
The objective of this study is to find the relationship between lactic acidemia and cerebral ischemia in aneurysmal subarachnoid hemorrhage causing vasospasms.
Methods: Lactic acid levels were measured using arterial blood gas analyzer as part of the clinical evaluation of patients presenting with computerized tomographic evidence of subarachnoid hemorrhage following rupture of intracranial aneurysms and traumatic brain injuries. Patients with CT evidence of significant intracranial mass effects (hydrocephalus, Hematomas) were excluded. Patients were stratified in to three groups based on Glasgow Coma Scale.
Results: 30 patients were included in each group and stratified according to Glasgow Coma Scale. The aneurysm group had mean lactic acid level of 2.7 mmol/l and the trauma group had 1.8 mmol/l. Stratification in aneurysm group showed 2.2 mmol/l, 2.7mmol/l and 3.2mmol/l in GCS 15-13, 12-9 and 8-3 groups respectively. Stratification in trauma group showed 1.6mmol/l and 2.1mmol/l in GCS 15-13 and 12-9 groups respectively. There were no trauma patients having GCS bellow 8.
Conclusion: Aneurysmal sub arachnoid hemorrhage has tendency to cause lactic acidemia than traumatic subarachnoid hemorrhage. vasospasm leading to ischemic injury in aneurysmal SAH is the likely pathophysiology.
Severity of the lactic acidemia shows a correlation with severity of cerebral dysfunction, so likely play a prognostic value.

Disclosures: **D. Lal:** None.

Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR266.12/V25

Topic: C.08. Ischemia

Support: NIH Grant 5R61HL159948
NSF Grant IIS-2123781

Title: Neuromuscular junction dynamics following ischemia associated with chronic kidney disease after nanostimulator-tethered stem cells enhanced treatment

Authors: *Y. AN, S. DING, H. KONG;
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Abstract: The neuromuscular junction is a specialized chemical synapse between motor neurons to skeletal muscles, and its dysfunction causes various muscle diseases. Ischemia, the severe peripheral artery disease, causes significant damage and changes to skeletal muscle homeostasis. Ischemia-induced disruption of vasculature leads to myofiber atrophy and damage to the neuromuscular junction. In particular, the ischemia associated with chronic kidney disease is challenging to treat because of skeletal muscle mitochondrial dysfunction caused by substantial decreases in mitochondrial oxidative phosphorylation or elevated mitochondrial reactive oxygen species with accumulated serum metabolites. In this study, we demonstrated that the nanostimulator-tethered stem cells enhanced treatment promoted vascularization in the hind ischemia mouse model associated with chronic kidney disease. We confirmed that enhanced perfusion recovery in the hind limb suppressed the damage in the neuromuscular junction. First, we tethered the mesenchymal stroma cells (MSCs) surface with poly(lactic-co-glycolic acid)-block-hyaluronic acid conjugated with integrin-binding RGD peptides (PLGA-HA-RGD) as a nanostimulator releasing tumor necrosis factor α (TNFα) and stimulating cellular secretory activity. HA-CD44 and RGD-integrin bonds increased the adhesion strength of nanosumulators to the cell surface, allowing them to remain stable during the injection. Following ischemic surgery with femoral artery ligation on a model of chronic kidney disease developed with a 0.2% adenine diet for four weeks, nanostimulator-tethering MSCs injected into the tibialis anterior and gastrocnemius muscle. We monitored the perfusion recovery using a laser doppler perfusion imaging system for four weeks after treatment and harvested the tissue from the tibialis anterior and gastrocnemius muscle in the second and fourth weeks. To quantitatively analyze the neuromuscular junction morphologies, we labeled the alpha-bungarotoxin as a postsynaptic marker and the synaptophysin as a presynaptic marker and acquired the fluorescence images using the confocal microscope. As a result, the perfusion in the hind limb was recovered in the treated group, and the morphologies of the neuromuscular junction and colocalization between presynaptic and postsynaptic maintained heathy conditions compared to the saline-injected

control group. In conclusion, the stem cells tethered with the nanostimulators improved vascularization and perfusion recovery and prevented neuromuscular junction damage following ischemic injury associated with chronic kidney disease.

Disclosures: **Y. An:** None. **S. Ding:** None. **H. Kong:** None.

Poster

PSTR266. Stroke: Models and Mechanisms

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Topic: C.08. Ischemia

Support: NRF (2019R1A2C1089108)
(MSIT) (No. 2022M3A9E4017151)
COMPA-2022C100

Title: Distinct Gene Expression Profiles in Human Cerebral and Coronary Artery Smooth Muscle Cells

Authors: *H.-S. KIM[1], S. LEE[2];
[1]Chonnam Natl' Univ., Gwangju, Korea, Republic of; [2]Chonnam Natl. Univ. Med. Sch. and Hosp., Gwangju, Korea, Republic of

Abstract: Background: Human cerebral artery smooth muscle cell layers exhibit unique embryologic, histologic, physiological, and pathological characteristics compared to coronary arteries, suggesting differential mechanisms for fatal outcomes, such as atherosclerosis. This study aimed to elucidate the differences in gene expression between human cerebral artery and coronary artery muscle cell layers. Methods: We obtained human vascular smooth muscle layers of the middle cerebral artery (MCA) and left anterior descending coronary artery (LAD) from the same individual through autopsy (n=10) and compared them using cDNA microarray (n=3). Microarray-based gene expression was analyzed using KEGG and Gene Ontology, and significant gene groups were validated for differential gene expression through qRT-PCR. We established cell lines through ex vivo culture and compared and confirmed the expression of genes related to vascular plasticity. Results: A total of 341 genes exhibited differential expression levels between the two blood vessels; 256 genes were upregulated, and 85 genes were downregulated in cerebral artery-derived vascular smooth muscle cells. Cerebral artery vascular muscle cells demonstrated higher expression of genes involved in angiogenesis, extracellular matrix, cell migration, neurogenesis, and inflammatory response compared to coronary arteries. Among the 256 upregulated genes, the top 13 genes are ApoD, Desmin, Claudin-11, and Netrin-1. According to KEGG and GO analysis, these genes were closely related to atherosclerosis, inflammatory cell migration, and retinal metabolism regulation signal transduction systems in the great arteries. Highly expressed gene clusters in the MCA were associated with type 2 diabetes mellitus (DM) and hypertension, which are well-known as major risk factors for atherosclerosis.

Finally, cell lines of human LAD and MCA established through ex vivo culture showed differences in gene expression related to vascular plasticity including cell cycle and contractility. Conclusion: Our study provides evidence of distinct gene expression profiles between human middle cerebral artery and coronary artery vascular muscle cells, offering insights into the differentiation of arterial function regulation and susceptibility to specific disease conditions. These findings can be utilized as a basis for further investigation, potentially leading to targeted diagnostic and therapeutic approaches for specific vascular diseases.

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

Poster

PSTR266. Stroke: Models and Mechanisms

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Program #/Poster #: PSTR266.14/W2

Topic: C.08. Ischemia

Support: NSTC111-2320-B-A49 -008
NSTC111-2320-B-A49 -037

Title: Modulating $GABA_A$ receptor function in cerebral ischemia-induced brain damage and dysfunctional plasticity

Authors: *H.-C. LIN, H. CHI, M.-C. CHU, C.-H. CHANG;
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Abstract: Stroke is now one of the most common cause of death and disability in the world. The pathological form of synaptic plasticity, ischemic long-term potentiation (iLTP) induced by oxygen and glucose deprivation (OGD), is implicated in the acute phase of stroke with the potentiation of N-methyl-D-aspartate receptor (NMDAR). While there has been widespread attention on the excitatory system, a recent study reported that γ-aminobutyric acid (GABA)ergic system is also involved in iLTP. In the present study, a brief exposure of OGD on the hippocampal slices and the induction of photothrombotic ischemia (PTI) were used as ex vivo and in vivo models of ischemic stroke, respectively. Here we propose that valproic acid (VPA), a histone deacetylase inhibitor, plays protective role against ischemic damage. Our results demonstrated that VPA treatment abolished hippocampal iLTP via enhancement of GABAA receptor and reduction of extracellular signal-regulated kinase (ERK) phosphorylation. Administration of VPA reduced brain infarct volume and motor dysfunction in mice with PTI. Moreover, VPA protected against ischemic injury by upregulating the GABAergic system, as well as downregulating ERK phosphorylation and matrix metalloproteinase in a PTI-induced ischemic stroke model. Our study demonstrated that VPA treatment rescued pathological form of synaptic plasticity following ex vivo OGD-induced ischemia and the brain infarct damage produced by in vivo PTI-induced ischemia. This study revealed the novel therapeutic impact of

VPA on ischemic stroke via restoring GABAergic deficits and the pathological hallmarks of ischemia.

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Poster

PSTR266. Stroke: Models and Mechanisms

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.15/W3

Topic: C.08. Ischemia

Support: 1R01NS127974-01A1

Title: Proteomic Response in Appalachian Emergent Large Vessel Occlusion Subjects Treated with Mechanical Thrombectomy

Authors: B. MAGLINGER[1], C. J. MCLOUTH[2], J. F. FRASER[3], H. S. HAZELWOOD[4], J. A. FRANK[3], S. PAHWA[3], J. P. HARP[4], D. DORNBOS, III[3], A. M. STOWE[4], A. L. TROUT[3], ***K. R. PENNYPACKER**[4];
[1]Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA; [2]Biostatistics, [3]Neurosurg., [4]Neurol., UNIVERSITY OF KENTUCKY, Lexington, KY

Abstract: Appalachia contains a subpopulation of the country that has gathered significant attention due to its healthcare accessibility, health disparities, and health outcomes. Individuals from Appalachia exhibit a higher incidence for stroke-related comorbidities including diabetes, obesity, and increased tobacco usage. The objective of this study was to identify proteomic biomarkers predictive of stroke outcomes specific to subjects residing in Appalachian counties. Eighty-one subjects met inclusion criteria for this study. These subjects underwent mechanical thrombectomy (MT) for emergent large vessel occlusion (ELVO), and systemic blood samples acquired at time of intervention were sent for proteomic analysis. Statistical analyses were then employed to examine whether the relationship between protein expression and outcomes differed by Appalachian status for functional outcomes (NIH Stroke Scale; NIHSS and Modified Rankin Score; mRS), cognitive outcomes (Montreal Cognitive Assessment; MoCA) and mortality. No significant differences were found in demographic data nor co-morbidities when comparing Appalachia to non-Appalachia subjects. However, time from stroke onset to treatment (last known normal) was significantly longer in patients from Appalachia. Comparison of Appalachia to non-Appalachian subjects revealed significant differences in functional/cognitive outcomes including NIHSS, MoCA, mRS, as well as neuroradiographic outcomes including infarct volume and edema volume. A comprehensive analysis of 184 cardiometabolic and inflammatory proteins revealed 13 proteins predictive of functional outcomes, 14 predictive of cognitive outcomes, six proteins identified were associated with mRS, and 7 proteins related to mortality. All these proteins were differentially correlated with these functions dependent on whether the patient was from Appalachia or non-Appalachian county. Our study utilizes an ELVO tissue bank and

registry to investigate the intracranial/intravascular proteomic environment occurring at time of thrombectomy. We found that patients presenting from Appalachian areas have a different proteomic response at the time of MT when compared to patients presenting from non-Appalachian areas. These differentially expressed proteins relate to stroke outcome and could be used as prognostic biomarkers, or as targets for novel therapies. The identification of a disparate proteomic response in Appalachian patients suggests a connection with environmental exposures. Further investigations through community-based studies are imperative to elucidate the underlying causes of this differential response.

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Poster

PSTR266. Stroke: Models and Mechanisms

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Topic: C.08. Ischemia

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NEXTGENERATIONEU and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)

Title: Stroke and Neural Dynamics: Exploring the impact of focal ischemic infarcts in the latent space

Authors: ***F. BARBAN**[1,2], M. NISHIMOTO[3], H. M. HUDSON[4], M. CHIAPPALONE[1,2], R. NUDO[4,5], D. GUGGENMOS[4];
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Abstract: Acquired brain injuries, such as stroke, are a leading cause of long-term disability worldwide. When an injury occurs within primary motor cortex (M1), it disrupts both the descending signals to the spinal cord controlling movement and the integration of somatosensory and premotor inputs leading to motor deficits. Luckily, the amount of impairment is not fixed, as some spontaneous recovery of function can occur and can be enhanced through rehabilitative therapies. The underlying mechanisms for recovery are still under investigation but are likely driven by reorganization in spared premotor (PM) and somatosensory (S1) regions. Understanding how these areas undergo neurophysiological changes following M1 injury is therefore crucial to understand the recovery process.
The purpose of this study was to determine: 1) whether neural population dynamics were

disrupted by the infarct within the sensorimotor network, and 2) if a loss of between-area activity and integration could be detected in the low-dimensional space. To investigate these questions, we employed a within-subject design. Twelve Long-Evans rats were trained on a skilled pellet retrieval task before receiving unilateral chronic 32-channel microelectrode array (MEA) implants in PM and S1. Neural data were recorded during task performance before and on Day 5 and Day 7 following a focal ischemic infarct in M1 and processed for single-unit spiking data. Gaussian Process Factor Analysis (GPFA) was used to estimate neural population dynamics, while Canonical Correlation Analysis (CCA) was employed to investigate sensorimotor integration. Additionally, classical metrics such as mean firing rate (MFR) and local variation of refractoriness (LvR) were calculated.
Our findings revealed that PM and S1 showed very similar MFR and LvR pre- and post-injury, indicating that by Day 5, there is a return to normal firing patterns. Despite this, the focal ischemic injury disrupted the task-related population dynamics in both areas. These perturbations in dynamics suggest that critical features of neural activity are represented in this low-dimensional embedding. Further, the task-related shared information between PM and S1 (as shown by CCA) was also disrupted. Taken together, the M1 lesion leads to a disruption in somatosensory-motor integration and task-related motor dynamics despite having little change in the underlying activity. Understanding of how spared areas reorganize activity to execute motor functions has the potential to shape the development of novel therapeutic approaches for individuals with acquired brain injuries.

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Poster

PSTR266. Stroke: Models and Mechanisms

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.17/W5

Topic: F.07. Biological Rhythms and Sleep

Support: Department of Veterans Affairs Merit Research Award I01BX002661
NIH Grant AA028175-01
MU Research Council (URD-22-006)

Title: Transient focal ischemia in middle aged mouse caused circadian desynchrony in the affected brain region

Authors: *A. CHISCHOLM[1], R. SHARMA[3], M. THAKKAR[4], M. PARIKH[2];
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Abstract: Background: Ischemic stroke (IS), the most common type of stroke, is the highest contributor to disability and fifth leading cause of mortality. Current treatment strategies are limited by time constraints and/or patient compliance, hence it is important that new therapeutic targets be identified to treat stroke. Circadian disruptions are the frequently observed in patient with stroke and are considered as unique, novel, and modifiable treatment target as these are associated with worse motor outcomes and slower functional recovery post-stroke. Circadian rhythms are controlled by a central clock located in the suprachiasmatic nucleus (SCN). Most of the physiological rhythms, including body temperature, sleep-wakefulness, are controlled by SCN and its entraining signals to the peripheral oscillators. These peripheral oscillators, present in all kinds of cells throughout the brain and periphery, regulates many non-circadian functions such as motor skills, memory and cognition. Hence, we hypothesized that IS affect circadian gene expression in the SCN and other affected brain region?**Methods**: To test our hypothesis, middle-aged C57BL/6J mice (10-12 months old) were used to target young adult human population. Under sterile conditions and inhalation (isoflurane) anesthesia focal cerebral ischemia was induced by middle cerebral artery occlusion (MCAO), via intraluminal technique, for 1h. In sham controls, similar surgery was performed except no occlusion was performed. Subsequently, animals were allowed to recover from surgical stress and left undisturbed. After 48h, animals were euthanized by decapitation and brain regions supplied by middle cerebral artery (MCA; motor cortex, striatum and hippocampus) were isolated from peri-infarct and contralateral region of the brain. In addition, SCN was also isolated. The tissues were processed for RT-PCR to examine the gene expression.**Results**: Our preliminary results showed that mice subjected to IS (N=4) displayed a) sensorimotor deficit mimicking human IS symptoms, b) Circadian desynchrony (CD) as evident by a significant reduction of Bmal1 gene expression in the motor cortex as compared to sham animals (N=4), however, no change was observed in the SCN. **Conclusion**: Our results suggest that that IS caused CD in middle aged mice. CD has the potential to interfere with the synchronization signals between the SCN and peripheral oscillators, potentially contributing to the development of various psychiatric and neurological disorders. Understanding the role of circadian genes in the post-stroke recovery process will help devise new and better therapeutic strategies for stroke rehabilitation.

Disclosures: **A. Chischolm:** None. **R. Sharma:** None. **M. Thakkar:** None. **M. Parikh:** None.

Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.18/W6

Topic: B.07. Network Interactions

Support: NIH Grant DA029718
NIH Grant RF1DA048808
NIH Grant U18DA052366

Title: Inhibition of iNOS Reduces Vasoconstriction from Chronic Cocaine in Mice Brain

Authors: *Y. LIU[1], Y. JETALPURIA[1], J. REN[2], Y. HUA[1], N. D. VOLKOW[3], Y. PAN[1], W. YIN[1], C. DU[1];
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Abstract: Cocaine is a highly addictive drug that can result in neurovascular complications such as transient ischemic attacks (TIA) and strokes. Neuroimaging studies have documented marked decreases in cerebral blood flow in the cortex of cocaine abusers. In preliminary studies in rodents, we observed that astrocytes in the brain contribute to cocaine-induced vasoconstriction and ischemic responses, which we hypothesized was associated with iNOS- (inducible Nitric Oxide Synthase) regulation. However, iNOS involvement in cocaine's vascular effects has not been studied. Here, we hypothesized that inhibition of iNOS expression could prevent cocaine-induced vasoconstriction and reduce cerebral ischemia. To test these hypotheses, we used ultra-high resolution optical coherent tomography (μOCT) to capture 3D vascular images from the prefrontal cortex (PFC) of mice before and after chronic cocaine treatment to compare the vascular changes in PFC including changes in vascular diameter and microvascular density. Specifically, three groups of animals were used: 1) wild type (WT) mice treated with cocaine (30mg/kg/day, i.p., for 14 days); 2) iNOS-Knock Out (KO) mice treated with cocaine (30mg/kg/day, i.p., for 14days); 3) wild type mice pretreated with L-NMMA (a non-specific NOS inhibitor, 40mg/kg/day, i.p.) 30 minutes prior to cocaine administration (30mg/kg/day; i.p., for 14 days). At Day 0, a cranial window was implanted on the area of the PFC, 3D optical angiography (μOCA) and cerebral blood flow images (μODT) in PFC were acquired at baseline and repeated at Day 16 (i.e., after 14 days cocaine treatment with one day withdraw). Comparing the neurovascular trees between Day 0 and Day16 (after chronic cocaine), our images observed cocaine induced vessel constriction in WT animals. However, vasoconstriction was reduced in iNOS-KO mice and L-NMMA-pretreated mice. Specifically, the vascular diameters were decreased ~15% in WT mice after chronic cocaine, but only ~7% and ~9% in iNOS-KO mice and L-NMMA-pretreated animals, respectively. The reduction of vasoconstriction effects of cocaine on iNOS-KO and L-NMMA-pretreated animals indicates iNOS's involvement in the vascular changes triggered by cocaine. Interestingly, we also observed increases in microvascular density more in iNOS-KO mice and L-NMMA-pretreated mice than in WT mice, indicating increase vessel recruitment or angiogenesis, which might help mitigate cocaine's vasoconstriction effects in CBF. These results indicated that iNOS plays an important role in cocaine-induced vasoconstriction and that inhibition of iNOS could therapeutically valuable for reducing cerebral ischemia risk in cocaine users.

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Poster

PSTR266. Stroke: Models and Mechanisms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.19/W7

Topic: H.05. Working Memory

Title: Effect of physical activity prior to cerebral ischemia on memory consolidation

Authors: *J. TOLEDO MOTTA, J. IBARRA HERNANDEZ, M. PERALES QUINTANA, V. NOVELO HERNANDEZ, S. GUTIERREZ ANGUIANO, D. ALVARADO LARA, K. PALOMO BARBOSA, M. SANTANA BRISEÑO;
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Abstract: Ischemic cerebrovascular disease is characterized by decreased blood flow that causes hypoxia and inflammation. The most reported sequelae are cognitive deficits and memory problems in up to 90% of the cases. Physical activity has been reported to increase the volume of the prefrontal cortex and the hippocampus, thereby improving memory. This study aimed to evaluate the effects of physical activity prior to a cerebral ischemia event on spatial memory in rats. Male Wistar rats (1 month old) were divided into four groups: 1) sedentary group, 2) exercise group, 3) sedentary-ischemia group, and 4) exercise-ischemia group. According to the group, the rats underwent a voluntary exercise program in a rodent wheel for 3 weeks where the distance and time invested per day were quantified. The Barnes maze test was used to assess spatial memory. After 4 days of training and short-term memory (STM) testing, the rats underwent bilateral common carotid artery occlusion for 15 min. After seven days, long-term memory (LTM) was assessed. The latency to find the escape box, number of successes and errors, and time spent in the escape box quadrant were analyzed using an ANOVA test. A $P<0.05$ was considered a significant difference. Physical activity had no significant effect on STM evaluation between groups. Physical activity decreased the latency to find the escape box during LTM evaluation compared to the sedentary group and increased the number of successes in finding the escape box ($P<0.05$); however, physical activity prior to cerebral ischemia increased the latency in which the escape box was found up to five times compared to the STM evaluation and was significantly higher compared to the other groups. In conclusion, our results show that exercise improves short- and long-term memory. However, in the ischemia groups, exercise showed increased latency compared to the sedentary group, which may be secondary to the structural changes that occur in the hippocampus due to aerobic exercise and vulnerability to ischemia-reperfusion injury.

Disclosures: J. Toledo Motta: None. **J. Ibarra Hernandez:** None. **M. Perales Quintana:** None. **V. Novelo Hernandez:** None. **S. Gutierrez Anguiano:** None. **D. Alvarado Lara:** None. **K. Palomo Barbosa:** None. **M. Santana Briseño:** None.

Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.01/W8

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01NS101108

Title: Temporal coding disruptions in the rat hippocamps following traumatic brain injury

Authors: *C. D. ADAM[1], E. MIRZAKHALILI[2], M. HABIB[2], J. A. WOLF[3];
[1]Univ. of Pennsylvania Neurosci. Grad. Group, Philadelphia, PA; [3]Neurosurg., [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Learning and memory deficits are commonly reported following traumatic brain injury (TBI) and often occur when TBI pathologies disrupt the neuronal circuits that normally support these processes. Learning and memory deficits are especially prevalent when the hippocampus and/or its afferent and efferent pathways are directly affected by TBI; however, the physiological mechanisms underlying these deficits are still poorly understood. To address this gap in knowledge, we subjected rats to a lateral fluid percussion injury (FPI) of ~1.8atm, implanted the injured hippocampus with high-density, laminar electrode arrays, and chronically recorded from awake rats as they explored a familiar and novel environment. Using current source density (CSD) we were able to localize specific layers within the CA1 region of the hippocampus and found a layer-specific loss of oscillatory power in TBI rats compared to sham-injured controls. We also found that theta-gamma phase-amplitude coupling (PAC) was drastically reduced in injured rats. Additionally, we found that individual units in injured rats were less entrained to the theta oscillation recorded in the local field potential. Using different spike features we were able to separate pyramidal cells and interneurons and found that interneurons in injured rats had a lower firing rate and drastically reduced entrainment to theta oscillations. These changes likely contribute to the loss of oscillatory power and PAC we observed, as interneurons are known to support the generation and interaction of theta and gamma oscillations in the hippocampus. When comparing firing properties across the familiar and novel environment, we found that there was a greater overlap in the number of pyramidal cells that were active in both environments in TBI rats compared to sham and that firing rates were more correlated between the environments in injured rats. Both results suggest a potential deficit in pattern separation, an important function attributed to the hippocampus. We are currently investigating how these TBI-associated physiological changes contribute to learning and memory behavior in a radial arm maze task. We are also characterizing differences between the hippocampus ipsilateral and contralateral to injury, and are investigating the effects of medial septal stimulation on learning and memory behavior and physiology. Preliminary results show that electrically stimulating the medial septum at theta frequency elicits a gamma frequency response in the hippocampus which could potentially be a means to artificially restore PAC lost from TBI.

Disclosures: C.D. Adam: None. **E. Mirzakhalili:** None. **M. Habib:** None. **J.A. Wolf:** None.

Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.02/W9

Topic: C.10. Brain Injury and Trauma

Support: T32NS043126
R01NS101108
I01RX003498

Title: Consistent effects of TBI on Hippocampal HFOs across small and large animal models

Authors: *E. MIRZAKHALILI, C. D. ADAM, A. V. ULYANOVA, H.-C. I. CHEN, V. E. JOHNSON, J. A. WOLF;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: High-frequency oscillations (HFOs) are believed to reflect synchronous activity of subpopulations of neurons. They have been extensively investigated in rodents and their role in memory functions is well-established, especially when they occur during sharp waves. Moreover, these oscillations have been proposed as biomarkers for neurological disorders in animal models as well as humans. We examined how HFOs are affected by traumatic brain injury (TBI) in small (male Long-Evans rats: 4 shams and 5 injured using Lateral Fluid Percussion injury model) and large (male Yucatan miniature swine: 3 shams and 3 injured using Controlled Cortical Implant injury model) animal models of TBI. We recorded chronically from the hippocampus of both animal models using laminar probes, and utilized our newly developed HFO detector to investigate how HFOs are affected by TBI. Our method uses continuous wavelet transform to detect HFOs using time-frequency maps and has been validated using benchmark datasets. We categorized the detected HFOs as ripples (80-250 Hz) and fast-ripples (250-500 Hz) and studied multiple metrics associated with these oscillations. In particular, we quantified the number of these events as well as the interval between the events, their duration, amplitude, and their oscillatory frequency. Our results indicate that the number of all HFO events in both animal models increases in injured animals. Consequently, the interval between the events also decreases. Our results indicated that the number of all high frequency events increased and consequently, the interval between the events decreased in injured animals. However, the average duration of an event, for both ripple and fast-ripple, did not change between groups. Yet, the average power of both ripple and fast-ripple events decreased in small and large animal models. The mean oscillation frequency also did not differ between sham and injured animals; however, the distribution between the two groups differed in that the distribution of the frequency for fast-ripples in injured group was more uniform and had lost its peaks. Collectively, these data suggest that traumatic injury disturbs the precise communications in the interconnected networks of the brain necessary for proper cognitive function. Future work will investigate how HFOs during sharp waves are affected by TBI. This would allow us to increase our understanding of how TBI can lead to cognitive impairment including memory dysfunction in humans and how therapies such as neuromodulation may help to resolve them.

Disclosures: E. Mirzakhalili: None. **C.D. Adam:** None. **A.V. Ulyanova:** None. **H.I. Chen:** None. **V.E. Johnson:** None. **J.A. Wolf:** None.

Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.03/W10

Topic: C.10. Brain Injury and Trauma

Support: NIH R01-NS124730
The Pittsburgh Foundation

Title: Reductions in hippocampal synaptic proteins associated with vesicular pool health in female and male rats after traumatic brain injury

Authors: A. ROBERTS[1], S. SVIRSKY[1], J. HENCHIR[1], M. PARRY[1], E. HOLETS[1], C. DIXON[1], T. C. JACKSON[2], ***S. CARLSON**[1];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. Florida, Gainesville, FL

Abstract: Traumatic brain injury (TBI) results in chronic functional impairments, including in cognitive, emotional, and somatic faculties, which may be mediated in part by impaired synaptic neurotransmission. We previously reported that a controlled cortical impact (CCI) brain injury significantly disrupts the vesicular pool at pre-synaptic nerve terminals. Through an improved understanding of the pathological mechanism(s) involved, this can facilitate development of improved therapeutic strategies for restoring neurotransmission. Dysregulation of endocytosis is a prime candidate as it functions to maintain the pre-synaptic vesicle pool through the process of recycling and replenishing vesicles. We hypothesize that traumatic brain injury (TBI) decreases the abundance of key endocytic machinery proteins post-injury. To test this, we compared the levels of hippocampal clathrin light and heavy chains, AP180, dynamin and Rab5 in CCI-injured (2.7mm, 4m/sec) or sham rats at 2wks post-injury. Synaptosomes were isolated from the female and male hippocampus (n=6 per sex per group) and synaptic levels of the target protein targets were measured by immunoblotting. TBI significantly reduced clathrin light chain, clathrin heavy chain, AP180, dynamin and Rab5 ($p<0.05$) in the hippocampus in tissues from both sexes. Synaptophysin was significantly decreased in male ($p<0.05$) but not in females post-CCI. These findings provide the first evidence of endocytosis protein changes after TBI, and highlight that changes in these key synaptic proteins are generalizable to both sexes. Ongoing work by our group is examining the impact of impaired endocytosis on altered neurotransmission after TBI, and to test if restoration of this novel pathway can improve neurobehavioral outcomes after experimental TBI.

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Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.04/W11

Topic: C.10. Brain Injury and Trauma

Support: NIH-NICHD Grant R37HD059288

Title: Interneuron regulation of inhibition in the hippocampus after traumatic train injury

Authors: *A. HERNANDEZ[1], B. N. JOHNSON[1], A. FARRUGIA[1], A. S. COHEN[2];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Children's Hosp Philadelphia, UPENN, Children's Hosp Philadelphia, UPENN, Bala Cynwyd, PA

Abstract: Traumatic brain injuries (TBI) afflict approximately two million people annually in the U.S. Many TBI survivors have chronic cognitive problems, which include deficits in learning and memory. Importantly, the hippocampus, a brain structure highly involved in learning and memory, is susceptible to impairment from TBI. A subregion of the hippocampus, area CA1, undergoes changes after TBI resulting in increased inhibitory synaptic transmission thereby leading to a decline in hippocampal network activation. However, the underlying circuit-mechanism that contributes to increased inhibition in area CA1 after injury is not well understood. The action potential firing of pyramidal neurons, the principal excitatory cells of CA1, is modulated by inhibitory interneurons. Indeed, reduced CA1 output due to augmented inhibition was demonstrated as a decrease in pyramidal neuron action potential firing, which was restored with the application of WIN55,212-2, a synthetic agonist of cannabinoid type 1 receptors (CB1R). The only interneuron that is cannabinoid sensitive and expresses CB1Rs are cholecystokinin interneurons (CCK INs). In fact, CB1Rs on CCK INs mediate depolarization induced suppression of inhibition (DSI) a phenomenon which serves to suppress GABA release from CCK IN onto pyramidal neurons. Since WIN can restore pyramidal neuron firing in injured slices and CCK INs are the only cannabinoid sensitive interneuron in area CA1, this work aims to investigate the changes in CCK IN inhibitory signaling and DSI after mild TBI using a well-validated lateral fluid percussion injury model of TBI and electrophysiology. We predict that mild TBI will increase CCK IN signaling, increasing their inhibitory input onto pyramidal neurons, and reduces DSI. This work will investigate the circuit-level mechanisms that contribute to the increased inhibition in hippocampal CA1 after TBI to further our understanding of the precise mechanisms by which injury drives learning and memory deficits to aid in the development of therapies for TBI survivors.

Disclosures: A. Hernandez: None. **B.N. Johnson:** None. **A. Farrugia:** None. **A.S. Cohen:** None.

Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.05/W12

Topic: C.10. Brain Injury and Trauma

Support: R01NS120099
R37HD059288

Title: Examining sex dependent effects on hippocampal shifts in excitability after mild traumatic brain injury

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Abstract: Traumatic brain injury (TBI) has steadily remained one of the leading causes of death and disability among young people worldwide. People commonly experience some level of cognitive impairment following traumatic injury that can last from days and weeks, to several months or even years. Animal studies have linked these cognitive impairments to opposing shifts in the excitability of different regions of the hippocampus, an important structure necessary for learning and memory. After injury there is a decrease in network excitability in area CA1 of the hippocampus of male mice that is associated with declined performance in a cognitive task. It is still unclear if the degree of cognitive impairment observed in males after injury would recapitulate in females. Thus, the goal of this project is to assess sex differences by examining hippocampal shifts in excitability after TBI. We model TBI using the lateral fluid percussion (LFP) injury device as this injury model mimics human TBI pathology in animals. We used a cohort of 6- to 8-week-old male and female C57BL/6 mice split into four groups: sham male, sham female, injured male, and injured female. Extracellular field recordings in the stratum radiatum of CA1 were conducted in ex vivo slices 6-10 days after LFP injury. We hypothesized and found that injured male mice had a decrease in area CA1 excitability after injury. On the other hand, preliminary data for injured female mice did not show a noticeable shift in excitability when compared to sham females. These results suggest that there might be sex dependent differences in TBI-induced shifts in excitability. Our findings serve to underscore the importance of considering possible sex differences in the pathophysiology of TBI in other contexts besides learning and memory.

Disclosures: I.A. Díaz Nieves: None. **A. Farrugia:** None. **A.S. Cohen:** None.

Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.06/W13

Topic: C.10. Brain Injury and Trauma

Support: UPMC Neurotrauma Endowed Chair Fund

Title: Controlled Cortical Impact Increases Hippocampal Epichaperome Formation in male and female rats.

Authors: S. SVIRSKY[1], Y. LI[1], J. HENCHIR[1], A. RODINA[2], S. W. CARLSON[1], G. CHIOSIS[2], *C. DIXON[1,3];
[1]Neurolog. Surgery, Univ. of Pittsburgh, Pittsburgh, PA; [2]Chem. Biol., Mem. Sloan Kettering Cancer Ctr., New York, NY; [3]VA Pittsburgh Healthcare Syst., Pittsburgh, PA

Abstract: Under normal conditions, heat shock proteins work in unison through dynamic protein interactions collectively referred to as the "chaperome." Recent work revealed that under conditions of cellular stress, the functional interactions of the chaperome are modified to form the "epichaperome," which results in improper protein folding, degradation, aggregation, and transport. This study is the first to investigate this novel mechanism of protein dyshomeostasis in traumatic brain injury (TBI). Male and female adult, Sprague-Dawley rats received a controlled cortical impact (CCI, 2.5mm deformation, 4m/sec) and the ipsilateral hippocampus was collected 24hrs 1, 2, and 4wks after injury (n=6 per injury/time-point/sex). The epichaperome complex was visualized by measuring HSP90, HSC70 and HOP expression in native SDS-PAGE and normalized to monomeric protein expression. A two-way ANOVA examined the effect of injury and sex at each time-point. Native HSP90, HSC70 and HOP protein expression showed a significant effect of injury effect across all time-points ($p<0.05$). Additionally, HSC70 and HOP showed significant sex effects at 24 hours and 4 weeks ($p<0.05$). Altogether, CCI increases epichaperome formation at all time points assessed between 24 hour and 4 weeks post-injury. Further investigation of this pathological mechanism can lead to a greater understanding of the link between TBI and increased risk of neurodegenerative disease and targeting the epichaperome for therapeutics.

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Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.07/W14

Topic: C.10. Brain Injury and Trauma

Title: Effects of traumatic brain injury combined with hemorrhagic shock on hippocampal synaptic plasticity

Authors: *K. E. BAHAMONDE, K. A. COAKLEY, C. M. ANDERSON, J. E. ORFILA, P. S. HERSON;
Dept. of Neurolog. Surgery, The Ohio State Univ., Columbus, OH

Abstract: Millions of Americans suffer from traumatic brain injuries (TBI), which is often suffered in combination with other injuries, including hemorrhagic shock. TBI and hemorrhage are common causes of morbidity and mortality in severe TBI and in combat, and often occur in combination. However, the influence of hemorrhagic shock on TBI outcomes and cognitive

recovery remains poorly understood. It is hypothesized that TBI and concurrent hemorrhagic shock mice will show greater memory impairment and reduced plasticity compared to either insult alone. This study used electrophysiology to assess memory impairments following a TBI with and without hemorrhagic shock. Extracellular field recording of the CA1 neurons in the hippocampus were performed to assess the effect of TBI and hemorrhagic shock on hippocampal long-term potentiation (LTP). Recordings were performed in acute hippocampal slices prepared 7 days and 30 days after injury. Under control conditions, a physiological theta burst stimulation (40 pulses, 100Hz) resulted in LTP that increased the slope of fEPSP to 171.5± 9.11% (n=10) of baseline. TBI injured mice and hemorrhagic shock only injured mice showed LTP of 167.5± 19.94% and 162.9± 6.44% respectively. There was no impairment present. The TBI and hemorrhagic shock injured mice had impaired LTP (122.0± 3.66%, n=5). This study is ongoing, and it hypothesized that there will be greater impairment in the TBI and hemorrhagic shock mice 30 days after injury. Preliminary data suggests that the TBI and hemorrhagic shock have impaired memory function and reduced long-term functional outcome 30 days post injury.

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Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.08/W15

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS131108
NIH Grant NS033310
NIH Grant NS100064

Title: Interrupted hippocampal-cortical coupling associated with the decline of learning and memory performance after posttraumatic epilepsy.

Authors: *X. TAO[1], U. DEVARAJ[2], R. STABA[2,3], A. BRAGIN[2,3], J. ENGEL, Jr.[2,3,4,5], L. LI[1,2]; [1]Univ. of North Texas, Denton, TX; [2]Dept. of Neurol., [3]Brain Res. Inst., Univ. of California Los Angeles, Los Angeles, CA; [4]Dept. of Neurobio., [5]Dept. of Psychiatry and Biobehavioral Sci., David Geffen Sch. of Med. at UCLA, Los Angeles, CA

Abstract: Impaired learning and memory is one of the neurobehavioral comorbidities of epilepsy, and understanding the underlying mechanisms may lead to improved therapeutics. The current study aims to explore the potential neuronal changes that lead to learning and memory impairment in a rodent model of post-traumatic epilepsy. In particular, we are interested in studying the changes in hippocampal-neocortical coupling due to the occurrence of pathological high frequency oscillations (pHFOs). This translational research focused on the latent period when no spontaneous seizure occurred. We used a traumatic brain injury (TBI) model of

temporal lobe epilepsy with microelectrodes implanted bilaterally in the neocortex, hippocampus, and striatum in thirty-three (n = 33) rats. A sham control group (n = 8) of age-matched naïve rats was used with the same electrode implantation assembly. Broadband brain electrical activity (1-3000 Hz) was recorded intermittently from day 1 of TBI until 21weeks after TBI. The experimental period of 3 to 21 weeks were used to identify which rats became epileptic (E+ group) and which did not (E- group).The Cheeseboard maze test was introduced to evaluate learning and memory performance before TBI, 2weeks, 3 months and 6 months after TBI. HFOs were detected and classified as pathological and physiological events by separating the ripple-on-spike (ROS) and ripple-without-spike (RWS) patterns, respectively. Coupling between hippocampal HFOs and prefrontal spindles was performed during the NREM sleep period over eight weeks. Neural correlates between hippocampal-neocortical coupling and behavioral performance were analyzed. The E+ group (n=14) demonstrated a significant ($p<0.001$) increase in hippocampal ROS rate compared to the E- and control groups. No changes in prefrontal spindles were found in the three groups. We observed a significant ($p < 0.001$) increase in synchrony between hippocampal ROS and prefrontal spindles in the E+ group (compared to the E- group), but not on RWS-spindle coupling. A strong correlation($r = 0.54$) was found between ROS-spindle coupling and decreased learning ability in E+ animals, but not in E- animals. Our data suggest a potential neural mechanism of impaired learning and memory in post-traumatic epilepsy. The normal memory consolidation process by the coupling of hippocampal ripples and prefrontal spindles was interfered by the occurrence of pHFOs. The hypersynchrony of pHFOs and prefrontal spindles may disrupt the normal process of memory consolidation. This study helps to improve our understanding of possible neural mechanisms of learning and memory difficulties in post-traumatic epilepsy.

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Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.09/W16

Topic: C.10. Brain Injury and Trauma

Support: R01 NS110898

Title: Sex-dependent cognitive dysfunction following repeated mild TBI in adolescent rats may rely on corticotrophin-releasing factor mediated alterations to the septo-hippocampal cholinergic system

Authors: *T. A. MCCORKLE, R. RAGHUPATHI;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Sports-related concussions (SRC, a subset of mild TBI) are a leading cause of long-term cognitive deficits in adolescents. Previously, we reported that repeated mild injuries in adolescent male and female rats resulted in spatial memory deficits in the novel object location task at 1-and-4-weeks post-injury in male rats. Female brain-injured animals, however, only showed impairment at 4-weeks. Since moderate TBI and chronic stress in animals lead to alterations in the expression of choline acetyltransferase (ChAT) and corticotrophin releasing factor (CRF) within the medial septum (MS), respectively, we hypothesized that disrupted cholinergic transmission between the MS and hippocampus may be the mechanistic basis for impairments in hippocampal-dependent memory, and that CRF expression in the amygdala regulated ChAT expression in the MS. Following behavioral assessment at each time point, rats were sacrificed for quantitative real-time PCR and immunohistochemistry. Our data demonstrated that there is a decrease in ChAT immunoreactivity in the MS of male brain-injured animals at 1-and-4-weeks, but fewer ChAT(+) cells were observed in female brain-injured animals only at the 4-week time point. While there was no significant difference in CRF mRNA expression in the amygdala or MS for either sex at either timepoint, injection of a CRFR1 antagonist into the MS of brain-injured animals showed an attenuation of the cognitive deficit and of the reduction in ChAT+ cells in female brain-injured animals only. In contrast, the CRFR1 antagonist did not reverse cognitive deficits in male brain-injured animals, and it impaired spatial memory in male sham-injured animals. Together, these data demonstrate that the role of CRF in altering cognitive functioning post-injury may be sex dependent. Further, they provide novel associations between ChAT and CRF expression and cognitive impairments following mild TBI, offering further insight into a potential mechanism of action in SRC.

Disclosures: T.A. McCorkle: None. **R. Raghupathi:** None.

Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.10/W17

Topic: C.10. Brain Injury and Trauma

Support: DoD W81XWH-21-1-0684
NIH R01NS097750
NIH R01NS069861

Title: Toll-like receptor 4 and matrix metalloproteinase-9 signaling contribute to synaptic and circuit alterations in the hippocampal dentate gyrus after brain injury.

Authors: *D. SUBRAMANIAN[1], E. CONTRERAS[2], L. DOVEK[3], V. SANTHAKUMAR[2]; [1]UC Riverside, Riverside, CA; [2]Mol. Cell and Systems Biol., Univ. of California, Riverside, Riverside, CA; [3]Univ. of California, Riverside Biomed. Sci. Grad. Program, Riverside, CA

Abstract: Traumatic Brain Injuries (TBI) often trigger a robust immune response characterized by the activation of inflammatory mediators that subsequently result in cell death, altered neuronal excitability, memory deficits and promotes epileptogenesis. We recently identified a key role for Toll-like receptor 4 (TLR4), an innate immune receptor, in augmenting posttraumatic network excitability. Importantly, pharmacological inhibition of TLR4 within the first 48 hours after TBI effectively reduced epileptogenesis and memory deficits in rodents. Here we examined whether TLR4 signaling recruits Matrix Metalloproteinase-9 (MMP-9), a potent Zn^{+} activated endopeptidase critically involved in circuit remodeling, and if the TLR4: MMP-9 signaling axis alters circuit function in the hippocampal dentate gyrus (DG) after concussive brain injury. Rats (p24) subjected to moderate lateral Fluid Percussion Injury (l-FPI) or sham injury were treated with antagonists of TLR4 (CLI-095, 0.5mg/kg, i.p.), MMP-9 (SB-3CT, 50mg/kg, i.p.) or vehicle 30min to 24hrs post-injury and examined at 48 hrs for MMP-9 activity. *In situ* zymography revealed an increase in MMP-9 activity 48 hrs after l-FPI, which was reduced by CLI-095 treatment. Early (1week post injury) and long-term (6-8 weeks post injury) changes in DG Granule Cells (GC) synaptic inputs were examined using whole-cell patch clamp technique. We observed an increase in the frequency of spontaneous excitatory postsynaptic currents and a decrease in spontaneous inhibitory postsynaptic currents to GCs 1 week and 6-8 weeks post-injury. Interestingly, these changes were prevented by early treatment with either CLI-095 or SB-3CT. In vivo recordings from urethane anesthetized rats showed an increase in perforant path evoked DG excitability one week after l-FPI, which were reduced by treatment with CLI-095 or SB-3CT. Together, our results suggest a TLR4 mediated increase in MMP-9 activity after TBI and identify a role for TLR4:MMP-9 signaling in altered dentate excitability following TBI.

Disclosures: D. Subramanian: None. **E. Contreras:** None. **L. Dovek:** None. **V. Santhakumar:** None.

Poster

PSTR267. Brain Injury: Effects in Hippocampus

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.11/W18

Topic: C.10. Brain Injury and Trauma

Support: R37 HD059288
R01 NS120099

Title: Investigating the Effects of Microglial Depletion on the Hippocampal Circuitry after Acute Mild Traumatic Brain Injuries.

Authors: *S. A. S. DELCY[1], A. M. FARRUGIA[2], A. S. COHEN[3];
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Abstract: Traumatic Brain Injury (TBI) affects 69 million people worldwide, and approximately 2.5 million in the United States alone. TBI is defined as a force or blow to the head and involves two distinct phases. In phase 1, tissue is damaged due to initial impact, whereas phase 2 includes secondary injury cascades and physiological changes that take place as a result of the primary injury. Neuroinflammation is a common immune response observed post-TBI that can result in neuronal death when prolonged. This phenomenon is not fully understood; however, scientists have reported that increased microglial response leads to increased inflammation in the brain, which contributes to secondary injuries. Furthermore, microglial activation may contribute to excitability shifts in the hippocampus due to cytokines and chemokines being released. Interestingly, the Cohen lab has reported increased network excitability in the dentate gyrus (DG) and decreased network excitability in area CA1. These regional hippocampal shifts in excitability contribute to deficits in learning and memory post TBI. Recent findings suggest that pharmacologically depleting microglia, using a CSF1-R inhibitor, improves TBI symptoms; however, little is known about physiological changes post-depletion. Given the relationship between microglial activation and neuroinflammation and the excitability shifts post-injury, this study investigates the role of microglial activation in physiological alterations in the hippocampal circuit to (1) better understand TBI pathophysiology and (2) introduce potential therapeutic targets to mitigate cognitive deficits post-injury. Preliminary results suggest that microglial depletion post-injury decreases neuroinflammatory factors which in turn reduce excitability shifts and improve learning. Future directions include depleting and repopulating microglia post-TBI; there are homeostatic/defensive properties associated with regenerated microglia which could further improve recovery of surviving neurons and restore E/I balance in the hippocampal circuitry. The proposed studies have the potential to introduce microglial depletion and repopulation as a therapeutic measure for chronic neuroinflammation and neuronal cell death which are both contributors of secondary injury presentation.

Disclosures: S.A.S. Delcy: None. **A.M. Farrugia:** None. **A.S. Cohen:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.01/W19

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Spinal Cord Injury Research Board of the New York State Department of Health C34462GG

Title: High-frequency rTMS artifact filtering from surface EMG

Authors: *M. BAYRAM[1,2,3], N. BRIHMAT[1,2], S. SALEH[2,1], G. H. YUE[1,2], J. ZHONG[4], G. F. FORREST[1,2];
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Sch., Newark, NJ; [3]Biomed. Engin., Acibadem Univ., Istanbul, Turkey; [4]Burke Med. Res. Inst., White Plains, NY

Abstract: INTRODUCTION: Repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive exploratory and neuromodulatory technique, has shown therapeutic effects not only in animal models, but also in individuals with spinal cord injury (SCI). Recently, high-frequency rTMS (HF-rTMS; >1 Hz) effect on corticospinal excitability has also been investigated in SCI with promising outcomes for recovery. However, depending on the rTMS repetition rate, recording meaningful Motor Evoked Potential (MEP) responses can be challenging due to the presence of rTMS and movement artifacts, which is further magnified using a HF-rTMS protocol wherein the artifacts could overshadow the actual MEP. This retrospective study evaluated the application of narrow notch filters to only remove the HF-rTMS artifacts without altering the MEP responses.
METHODS: With a study protocol approved by the local Institutional Review Board, HF-rTMS was delivered in 10 trains of 75 biphasic stimuli at 15 Hz, through a B65 figure of eight coil connected to a MagPro X100 stimulator, at suprathreshold stimulus intensities ranging from 80 to 110% of the individual resting motor threshold. The analysis included offline data of 94 sessions, obtained from 12 individuals (6 SCI and 6 able-bodied). Continuous surface EMG data recorded from forearm muscles were first band filtered at 20-350 Hz. A narrow notch (4th order Butterworth with 3 dB stopband) filter with a center frequency of 15 Hz and a width of 1 Hz was then applied, together with its 4 harmonics, immediately before the 75 stimuli train.
RESULTS: Preliminary results showed that, regardless of the HF-rTMS intensity and the population studied, the stimulation artifacts were on average reduced (-32 dB), with minimal negative impact on the MEP amplitude response ($\leq$ - 7%).
CONCLUSION: Removing HF-rTMS artifact might be of interest, particularly with data where MEP response is the main outcome and thus could be overestimated due to the artifact. The filtering strategy seems promising to obtain cleaner EMG data. Further analysis is needed to verify the preliminary results, with rTMS applied at different repetition rates.

Disclosures: **M. Bayram:** None. **N. Brihmat:** None. **S. Saleh:** None. **G.H. Yue:** None. **J. Zhong:** None. **G.F. Forrest:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.02/W20

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Spinal Cord Injury Research Board of the New York State Department of Health (C34462GG)
Tim Reynolds Foundation

Title: Repetitive Transcranial Magnetic Stimulation Intensity versus Number of Bursts Effects on Corticospinal Excitability in Able-Bodied and SCI-Affected Individuals

Authors: *N. BRIHMAT[1,2], M. B. BAYRAM[2], S. H. SALEH[3], J. ZHONG[4], G. H. YUE[5,1], G. F. FORREST[2];
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation strategy with a potential to induce neuroplasticity and reinforce the residual spinal and supraspinal pathways after a CNS injury. Recent and increasing evidence suggests the benefits of high-frequency rTMS (HF-rTMS) to boost functional recovery in individuals with spinal cord injury (SCI). The stimulation parameters, such as the stimulation intensity (SI) and the number of bursts (nB), are known to affect the motor evoked potential (MEP) responses recorded from the targeted muscle. Our goal was to investigate how the modulation of these parameters affect the rTMS responses in uninjured and spinal cord injured individuals. We used surface EMG data recorded continuously from hand and forearm muscles of 4 able-bodied (AB) and 6 chronic SCI individuals, during the administration of a HF-rTMS protocol (75 pulses per burst, 15 Hz, B65 figure-of-eight coil connected to a MagPro X100/X30 machines). During the first visit (V1), the participants from the two groups were administered single bursts of HF-rTMS at different SI (**AB**: 90-100-105%; **SCI**: 80-90-100-105%, of the individual resting motor threshold, RMT), to test the participant tolerability. During the following visit (V2), the participants were administered 10 bursts at the same SI, defined during V1, with a 60 sec inter-train interval for 10 min. MEPs were extracted from the targeted muscles EMG and their amplitude modulation analyzed across bursts using the TMS Analysis Toolbox. An intensity-dependent effect was observed with the data from the AB and SCI individuals at V1. The HF-rTMS SI significantly affected the MEP amplitude across bursts with a progressive increase of the MEP amplitude with the SI used. No such effect was observed when increasing the nB. These results show that increasing the number of bursts, unlike increasing the SI, does not result in the concomitant and continuous increase of MEP amplitude. This finding needs to be considered when planning HF-rTMS for therapeutic purposes.

Disclosures: **N. Brihmat:** None. **M.B. Bayram:** None. **S.H. Saleh:** None. **J. Zhong:** None. **G.H. Yue:** None. **G.F. Forrest:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.03/W21

Topic: C.11. Spinal Cord Injury and Plasticity

Support: RERC #90RE5021-01-00
Tim Reynolds Foundation
Ritholz Foundation

Title: Effects of gait symmetry with spinal cord transcutaneous stimulation on muscle activity in individuals with SCI

Authors: *M. ANJARIA[1], K. MOMENI[2], M. RAVI[1], A. BHEEMREDDY[1], M. B. BAYRAM[1], S. HABER[1], G. FORREST[1];
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Abstract: A previous study by our group showcased that use of optimal and individualized spinal cord transcutaneous stimulation (scTS) parameters during overground gait training facilitate coordination in kinematics profiles in individuals with incomplete spinal cord injury (SCI). We extended our work to evaluate the immediate motor response changes from stimulation and the motor response after scTS combined with gait training. Three-dimensional kinematics were evaluated for several chronic incomplete SCI participants who completed gait training with and without scTS along with multi-channel EMG analysis. Multiple, targeted cohorts of scTS were delivered using cathodes at the lumbosacral and thoracic spinal sites and several sites for anodes. The stimulation waveforms consisted of a rectangular pulse (width of 1ms) with 5kHz carrier frequency. Individuals were tested before, at midpoint and after training. Full-body kinematics (Motion Analysis, California) were collected while participants walked overground with and without scTS and surface EMG electrodes (Motion Lab Systems Inc., Baton Rouge, LA) for muscle activation were collected for both upper and lower extremity muscle groups. For scTS trials, there was an immediate effect on the intralimb and interlimb coefficient of variation for lower-extremity muscle groups compared to trials without scTS. Moreover, when trials of overground gait training combined with stimulation were compared to trials with stimulation but no prior training, the results showed reduced interlimb coefficient of variation in muscles corresponding to spinal stimulation sites. These changes suggest that voluntary motor gains persisted with trials without stimulation, demonstrating the effectiveness of targeted scTS + training, and its sustenance post training, across the participant population. Moreover, further gains were observed up to 2 years post training. The data shows the immediate impact to the spinal excitability through neuromodulation and its longer-term impact when combined with training to include the peripheral circuitry.

Disclosures: **M. Anjaria:** None. **K. Momeni:** None. **M. Ravi:** None. **A. Bheemreddy:** None. **M.B. Bayram:** None. **S. Haber:** None. **G. Forrest:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.04/W22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Tim Reynolds Foundation
NIDILRR (RERC #90RE5021 01 00)

Title: Analysis of Spinal Cord Transcutaneous Stimulation induced EMG Responses in individuals with Intrathecal Baclofen Pump after SCI

Authors: *M. RAVI[1], K. MOMENI[2], A. BHEEMREDDY[1], M. ANJARIA[1], M. B. BAYRAM[1], J. LOPEZ[3], S. KIRSHBLUM[3], G. F. FORREST[1];
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Abstract: Approximately 18,000 people in the United States alone suffer a Spinal Cord Injury (SCI) each year. SCI affects the nervous system in several ways including causing affected individuals to suffer loss of mobility and sensation below the level of lesion. One major secondary medical complication associated with SCI is spasticity and it affects up to 65% of people with SCI. Spasticity is characterized by involuntary muscle contractions and increased muscle tone that can interfere with daily activities, mobility, and sleep in addition to causing pain, contractures, stress, and reduced quality of life. One common intervention for severe spasticity is an Intrathecal Baclofen (ITB) pump delivery system. Spinal Cord Transcutaneous Stimulation (scTS) has been shown to significantly improve sensorimotor function in addition to improving some secondary effects of SCI including stabilizing blood pressure and decreasing spasticity. To our knowledge, no other scTS studies have been performed on people with an implanted ITB system. In this study, we examine the scTS induced Electromyography (EMG) responses on people with an implanted ITB pump after SCI and compare them with responses for people without an ITB pump after SCI. We recruited individuals with SCI (both complete and incomplete) and applied scTS with T11-12 spinal segment as cathode and bilateral Anterior Superior Iliac Spine (ASIS) as anode. Carrier-wave frequency was set at 5 kHz for monophasic waveform and EMG was recorded from key lower limb muscles. The amplitude of scTS was modulated systematically and EMG responses corresponding to each amplitude were analyzed for all bilateral lower limb muscles. The responses were also analyzed by latency - Early response (<15ms after stimulation pulse), Late response (15-60ms) as well as for Whole response (0-60ms after stimulation pulse). Results of the analyses show that the peak-to-peak EMG responses (early, late and whole) for individuals with an SCI + ITB system were significantly lower than the responses for individuals without the ITB system. Therefore, the amplitude at which scTS is delivered may have to be different for those with an implanted ITB pump due to reduced responsiveness caused by presence of Baclofen in the nervous system. Further research is needed to establish safety and efficacy of scTS neuromodulation for multiple spinal sites, amplitudes, and frequencies for individuals with an ITB pump.

Disclosures: M. Ravi: None. **K. Momeni:** None. **A. Bheemreddy:** None. **M. Anjaria:** None. **M.B. Bayram:** None. **J. Lopez:** None. **S. Kirshblum:** None. **G.F. Forrest:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.05/W23

Topic: C.11. Spinal Cord Injury and Plasticity

Support: RERC #90RE5021-01-00
Tim Reynolds Foundation
Ritholz Foundation

Title: Effects of Spinal Cord Transcutaneous stimulation and Activity-Based Training on Spasticity

Authors: *A. BHEEMREDDY, M. ANJARIA, M. B. BAYRAM, M. RAVI, F. ZHANG, S. HABER, G. F. FORREST;
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Abstract: Spasticity is a common movement disorder that develops in 65-70% of individuals following a spinal cord injury (SCI) within one-year post-injury. Current methods to manage severe spasticity involve pharmacological treatments that have been shown to have concomitant side effects that can limit participants' ability to respond to neurorehabilitation. Spinal cord transcutaneous stimulation (scTS) in addition to activity-based therapy (ABT) have been shown to be effective interventions for neurorehabilitation to improve function for people with SCI. We hypothesize that longitudinal targeted scTS + ABT will also have a beneficial effect on spasticity for SCI. Targeted scTS + ABT incorporated exoskeleton and overground gait training. Specific scTS parameters for training were selected based on mapping sessions that systematically modulated stimulation frequencies, amplitudes, and spinal site locations. Surface Electromyogram (EMG) electrodes (Motion Lab Systems Inc., Baton Rouge, LA) were placed on muscles of the lower extremity before and after completion of the training to analyze muscle activation during overground walking tests performed out of suit. Immediate and long-term substantial reduction in lower limb spasticity was determined from analyses of muscle activation data pre and post intervention protocol. Power spectrum analyses on the EMG collected during walking determined a clear distinction following longitudinal scTS and ABT, showing substantial reduction in peak and average power in the frequency domain for the EMG data. These results show the potential for scTS + ABT as an effective intervention for reducing spasticity while also improving voluntary movement following SCI.

Disclosures: A. Bheemreddy: None. **M. Anjaria:** None. **M.B. Bayram:** None. **M. Ravi:** None. **F. Zhang:** None. **S. Haber:** None. **G.F. Forrest:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.06/W24

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NJCSCR Grant CSCR23ERG001
NIDILRR Grant RERC 90RE5021-01-00
NIDILRR Grant ARRT 90ARHF0002
the Tim Reynolds Foundation

Title: Combining Spinal Cord Transcutaneous Stimulation with Activity-based Training in Inpatient Settings to Improve Upper Extremity Function Following Cervical Spinal Cord Injury

Authors: *F. ZHANG, J. CARNAHAN, A. BHEEMREDDY, M. RAVI, M. ANJARIA, G. FORREST;
Kessler Fndn., West Orange, NJ

Abstract: Initiating rehabilitation at an early stage following spinal cord injury (SCI) is critical and delayed interventions may limit the ultimate functional recovery. Current rehabilitative therapies focus on promoting activity-dependent neuroplasticity by involving functional and task-specific activities with high intensity and high repetition. Spinal cord transcutaneous stimulation (scTS) is a novel, non-invasive technique that can neuro-modulate the excitability of spinal circuits and facilitate the weak or silent drive for restoration of motor and sensor function after SCI. Combining scTS with activity-based training (ABT) as a daily therapy in an inpatient program holds great potential to increase the rate of functional and neurological recovery before the chronicity and emergence of new types of pathology influence long-term recovery. The goal of this study is to assess the safety and preliminary efficacy of the scTS+ABT intervention in an inpatient rehabilitation program, to facilitate upper extremity (UE) functional recovery for individuals with acute to subacute cervical SCI. Individuals with acute to subacute cervical SCI were randomized to receive scTS+ABT, $scTS_{sham}$+ABT, or ABT alone. The interventions were administered over 2 consecutive weeks, for 30mins per session and 5 sessions per week, as a part of the daily 3-hour therapy. ABT focused on activities of grasping, pinching, and gross and fine motor skill. Participants in scTS+ABT received ABT while receiving concomitant, active scTS applied at the cervical and thoracic spinal segments over the dorsal skin with optimized and customized stimulation parameters. The sham-control group went through ABT paired with sham stimulation to control for placebo effects associated with the perception of scTS. The type, frequency, and severity of adverse event reports (related to scTS, ABT, and SCI) during the intervention course were reported to determine whether scTS+ABT is safe and feasible when applied during an inpatient rehabilitation program. In addition, we quantitatively assessed UE motor impairment, maximum voluntary handgrip strength, and functional ability at pre- and post-intervention to evaluate the efficacy of scTS+ABT in promoting UE functional recovery in acute to subacute SCI, as compared to the sham control and ABT only. The research findings could provide evidence for integrating scTS+ABT into inpatient rehabilitation practice, which will significantly accelerate the functional and neurological recovery of acute and subacute SCI in the current clinical care.

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Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.07/W25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Improvement of voluntary movement following task-specific training with subthreshold lumbosacral epidural stimulation in individuals with severe spinal cord injury.

Authors: *C. ANGELI[1,2], E. REJC[1,2], G. FORREST[2], S. HARKEMA[1];
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Abstract: Recovery of voluntary motor function several years after clinical diagnosis of motor complete spinal cord injury (SCI) is rare. Subthreshold network targeted lumbosacral epidural stimulation (scES) has been previously shown to restore voluntary movement in individuals with motor complete SCI (Angeli et al. 2014, Grahn et al. 2017, Darrow et al. 2022). The aim of this study is to determine the effects of task-specific training with scES on voluntary movement ability in individuals with severe SCI.Individuals with chronic motor complete SCI (n=27) were implanted at L1-S1 spinal cord level with an electrode array and neurostimulator. These individuals (age: 35.5 ± 10.6 yrs; time post-injury: 10.1 ± 8.1 yrs; 37% female, 15 AIS A, 11 AIS B, 1 AIS C) were unable to move their legs voluntarily or stand independently. Voluntary movement mapping was performed in all participants while asking individuals to attempt flexion movements of the first toe, ankle and hip. Further changes in parameters were dependent on the observed EMG modulation and joint movements. Individuals were randomized to a voluntary training group (Vol-scES) or a cardiovascular group (CV-scES). Individuals used scES for 6 hours a day practicing voluntary movement (Vol-scES) or for blood pressure regulation (CV-scES). We performed torque and EMG assessments in a dynamometer pre and post training with voluntary specific stimulation.All individuals were able to modulate EMG activity in the presence of scES and were able to move at least one joint. There was no difference between groups prior to the start of the training intervention. Individuals randomized to the Vol-scES group showed an improvement in maximum torque generation and ability to perform multiple consecutive repetitions of hip flexion when compared to their baseline (post-implant, pre-intervention values). While individuals randomized to the CV-scES group showed a slight decrease in both outcomes. When asked to perform ankle dorsiflexion the median RMS value of TA showed a slight increase for the VoL-scES group with a decrease for the CV-scES group. Torque generation during dorsiflexion increased in the VoL-scES post training while there was a decrease in the CV-scES. These results provide evidence that task-specific training with scES results in greater voluntary movement ability. Further, scES modulates network excitability of the injured spinal cord to allow for the integration of afferent and supraspinal descending input to generate movement below the injury after severe SCI.

Disclosures: C. Angeli: None. **E. Rejc:** None. **G. Forrest:** None. **S. Harkema:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.08/W26

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2016PG-MED001, Leona M. & Harry B. Helmsley Charitable Trust
ES_BI-2017, Christopher and Dana Reeve Foundation
University of Louisville Hospital

Title: High frequency blood pressure oscillations during orthostasis can occur independently of baroreflex-sympathoneural dysfunction in individuals with cervical spinal cord injury

Authors: *S. WANG[1], H. LEDBETTER[1], S. J. HARKEMA[1,2], D. S. GOLDSTEIN[3];
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Abstract: Introduction: Orthostasis often induces low frequency blood pressure (BP) oscillations (Mayer waves) that are related to altered baroreflex modulation of sympathetic cardiovascular outflow. Orthostasis also increases relatively high frequency (HF) oscillations at the periodicity of breathing. Whether HF oscillations of BP during orthostasis depend on baroreflex-sympathoneural function is poorly understood. Individuals with chronic cervical spinal cord injury (SCI) have orthostatic hypotension (OH) related to baroreflex-sympathoneural failure, providing an opportunity to fill this knowledge gap. **Methods:** Twenty-one participants with chronic cervical SCI and OH underwent 70° head-up tilt for up to 30', with continuous finger BP and electrocardiographic (ECG) monitoring. The respiratory period was estimated from amplitudes of ECG R waves. Power spectral density (PSD) was quantified from systolic BP, RR interval, and R wave amplitude during 5' supine and the first 3' of tilt (shorter if the tilt was tolerated less than 3'), using Welch's modified periodogram. HF spectral power of BP was calculated by integrating PSD in the respiratory frequency range (0.15-0.4 Hz). **Results:** HF spectral power of systolic BP increased in a majority of the participants, but due to individual variability the mean change was not significant ($p=0.1337$). In a subgroup ($n=14$) with a prominent peak in the PSD of respiratory activities, HF spectral power of systolic BP tended to increase from supine to tilt ($p=0.0586$). In the subgroup without a prominent peak in the respiratory PSD, HF spectral power of systolic BP did not change with tilt ($p=0.4820$). **Conclusions:** Individuals with chronic cervical SCI and OH often have tilt-evoked, breathing driven BP oscillations. Such oscillations therefore can occur independently of baroreflex-sympathoneural dysfunction, in contrast with Mayer waves.

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Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.09/W27

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Reynolds Foundation
Craig H Neilsen Foundation

Title: Modulation of Spasticity Using Epidural Spinal Cord Stimulation in Chronic Spinal Cord Injury

Authors: *G. FORREST[1], C. A. ANGELI[2], E. REJC[3], S. J. HARKEMA[4];
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Abstract: The evidence clearly indicates that spasticity is a significant issue for persons with SCI, and has a significant negative impact on the quality of life. Baclofen is a commonly used pharmacological treatment for spasticity. Unfortunately, such pharmacological approaches can produce side effects that include: drowsiness, dizziness, weakness, constipation, sleep disturbances, changes in the muscles innervated, or unintended degradation of voluntary movement. We hypothesized that targeting integrated networks may reduce the spasticity mechanisms, utilizing lumbosacral spinal networks when supraspinal input was chronically compromised. In this study, we neurophysiologically identify specific spinal and peripheral circuitry responsible for using neuromodulation to directly address spasticity in five individuals with chronic cervical SCI, implanted with a Medtronic 5-6-5 electrode array and neurostimulator to apply Epidural Spinal Cord Stimulation (scES). Spasticity was evident and induced in all individuals with SCI without scES when monitored while lying supine. Elicited spasticity induced by a trigger three times sequentially and recorded EMG activity of the hips, knees, and ankles without and with targeted scES. For stimulation, the frequencies ranged from 85 -120 Hz and relied on cathode selection of all but a few electrodes selected as anodes. Muscle activity (as recorded using EMG) was significantly reduced both in the number of bursts and level of activity in all muscles with targeted scES. These results demonstrate that neuromodulation specific to the lumbar spinal cord reduces spasticity in chronic human SCI. Integrated systematic neuromodulation at the lumbosacral spinal, such as scES, now has shown the ability to improve motor function and reduce spasticity, both devastating consequences after severe SCI, using the same epidural implantation method providing a potential multi-modality clinical treatment.

Disclosures: G. Forrest: None. **C.A. Angeli:** None. **E. Rejc:** None. **S.J. Harkema:** None.

Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.10/W28

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NINDS

Title: Effect of transcutaneous electrical spinal stimulation on clonus in humans with chronic spinal cord injury

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Abstract: Transcutaneous electrical spinal stimulation (TESS) has been used to improve voluntary motor output in humans with spinal cord injury (SCI). However, the effect of TESS on involuntary muscle activation patterns, such as clonus, after SCI remains poorly understood. To address this question, we tested the effect of 20 min of TESS (30Hz pulses with a 5kHz carrier frequency) applied between L1-L2 spinous processes on clonus measured in the soleus muscle using electromyographic (EMG) activity in five individuals with chronic cervical SCI. During testing, participants were seated with their hips at 90° and the knee angle ~110°. Clonus was induced with a rapid dorsiflexion stretch of the ankle plantar flexors by an experimenter. Using EMG burst onsets and offsets, we quantified clonus duration, number of bursts, burst frequency, burst duration, interburst duration (i.e., a period of a decrease or a relative silence following the burst of EMG), and burst amplitude for each individual trial. We found that before TESS the median clonus duration was 26.0 sec (range 4.1-45.7 sec), number of bursts was 130 (range 21-229), burst frequency was 4.9 Hz (range 4.9-6.3 Hz), burst duration was 58.68 ms (range 50.9-86.3 ms), interburst duration was 114.8 ms (range 110.4-142.2 ms), and burst amplitude was 0.2 mV (range 0.2-0.4 mV) (n=5). A Wilcoxon signed-rank test found significant reductions in clonus duration (p=0.04), number of bursts (p=0.04), and burst amplitude (p=0.04) following TESS. In two out of five individuals tested, clonus was completely abolished immediately after TESS and the suppression lasted for several hours. In the other three individuals tested, there was a decrease in the median clonus duration (from 36.0 to 7.4 sec), number of bursts (from 200.3 to 37.3), and burst amplitude (from 0.3 to 0.2 mV) following TESS. These results suggest that TESS can suppress and modulate ankle clonus following chronic SCI.

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Poster

PSTR268. Spinal Cord Injury: Neuromodulation Therapies II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.11/X1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 5R01NS099872-06

Title: Intraspinal vs. epidural targeted, activity-dependent spinal stimulation to improve forelimb function after chronic cervical spinal cord injury

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Abstract: Cervical spinal cord injuries (SCI) can damage motor pathways that control movements of the hands and arms and which can have devastating long-term health and financial consequences. We are developing a novel therapy for chronic SCIs that uses targeted activity-dependent electrical spinal stimulation (TADSS) to improve motor recovery. We previously showed that intraspinal TADSS synchronized to volitional contractions of an impaired forelimb muscle improved performances of rats in a reach-and-grasp task. For this study, we wanted to compare intraspinal microstimulation which can precisely target specific motor pools with epidural stimulation in a chronic cervical spinal cord injury model. Epidural stimulation would be easier to implement in humans since it is substantially less invasive and therefore involve less surgical risk to the patient. We also want to understand the mechanisms that drive recovery in animals that receive TADSS therapy by using electrical stimulation of motor cortex and recording evoked potentials in the spinal cord. For these experiments, four week after a moderate-severe cervical SCI, rats were implanted with an array of penetrating platinum iridium microwires in the ventral horn of spinal segments C5-C7 or an epidural array of electrodes, as well as wires in 3 muscles of the impaired forelimb for electromyographic (EMG) recording which were used to trigger spinal stimulation. Animals also had electrodes implanted over motor cortex and the strength of the cortically evoked potentials were assessed during the therapy period. Starting 2 weeks after implantation, male and female rats received therapy for 5 weeks. During the therapy period, TADSS animals received 3-channels of closed-loop spinal stimulation contingent on muscle activity of the impaired forelimb muscles. For 5 hours per day, including during reaching tasks, EMG from each muscle triggered sub-movement-threshold stimulation through a spinal electrode that could elicit contractions of that muscle with higher stimulus currents. Non-stimulated control animals received only behavioral training. Periodically, animals underwent cortical stimulation and evoked potentials were recorded in the spinal cord with the electrodes used for therapy. Epidural and intraspinal stimulation were both effective at restoring reaching performance in females but was not as effective at promoting recovery in males. In animals that received TADSS therapy, there was potentiation of the evoked potentials. These results demonstrate optimizations for long term functional benefits of TADSS and suggest that strengthening descending pathways that survived the injury is driving recovery.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.01/X2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Todd Crawford Foundation for Paralysis Cure
Crawford Scholar Fund
Kosair for Kids Center for Pediatric NeuroRecovery

Title: Unveiling the Impact of Spinal Cord Injury on the Pediatric Brain: Neuroimaging and Electrophysiological Findings

Authors: *L. ALVARADO, M. E. KING, B. E. DEPUE, A. L. BEHRMAN;
Univ. of Louisville, Louisville, KY

Abstract: Spinal cord injury (SCI) has far-reaching consequences that extend beyond the spinal cord, impacting supraspinal structures. While previous research has highlighted brain changes in adults with SCI, limited research exists on the effects of SCI on the pediatric brain. To address this gap, our study investigated neural changes in children with SCI using electrophysiology and neuroimaging techniques, aiming to understand the relationship between residual spinal transmission and supraspinal reorganization. The study included children with SCI aged 4 to 12 years who were at least one-year post-injury and in stable medical condition. Electrophysiological examination children with SCI (7 males, 2 females; mean age = 8.8 ± 2.2 years) showed some persistent supraspinal inputs to spinal motor circuitry despite complete SCI, supporting the concept of discomplete injuries and indicating that clinical assessments may underestimate residual sensorimotor function. The neural conduction of the corticospinal tract (CST) mediating volitional motor function was assessed via functional neurophysiological assessment. An acoustic startle response assessment tested the reflexive activity of the reticulospinal tract (RST). Finally, the functional transmission of the dorsal column-medial lemniscus pathway was evaluated by analyzing somatosensory evoked potentials. Neuroimaging showed reduced gray matter morphometry and functional connectivity in cortical and subcortical sensorimotor structures and lower CST microstructural integrity in children with SCI compared to 18 TD controls. There were no significant differences in age, BMI, or gender between the two groups, and neuroimaging quality control analysis indicated no statistically significant differences in motion-related artifacts. Correlation analyses revealed that higher cortical and subcortical measures were positively associated with increased CST activity, while elevated RST activity levels were linked to improved subcortical morphometry and functional connectivity. Our findings provide valuable insights into the quantifiable alterations in the pediatric brain resulting from disrupted neural transmission of spinal pathways. Moreover, our

study highlights the potential of neuroimaging techniques as biomarkers for assessing the progress of recovery and monitoring the effectiveness of interventions that aim to improve spinal translesional connectivity.

Disclosures: L. Alvarado: None. **M.E. King:** None. **B.E. Depue:** None. **A.L. Behrman:** None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.02/X3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Kosair for Kids Center for Pediatric NeuroRecovery
Todd Crawford Foundation for Paralysis Cure
Crawford Scholar Fund

Title: Child's Play: Successful Conduct of Neuroscience Focused Research in Children with Spinal Cord Injuries

Authors: *A. L. BEHRMAN, M. E. KING, L. ALVARADO;
Univ. of Louisville, Louisville, KY

Abstract: Conducting research with children can present unique challenges in ensuring valid outcomes. To address these challenges, we developed a child-centric approach building on published guidelines and implementing a three-component strategy: learn, play, practice. Twelve children, including eleven with spinal cord injury (ages 6-15 years) and one typically developing child (age 7), participated in neurophysiology assessments of spinal pathways and magnetic resonance imaging (MRI) of brain morphology and connectivity. Each assessment lasted approximately 1.7 hours on average. To facilitate the learning component, we created a comicbook that provided detailed explanations of each assessment and introduced the participants to the functions of the nervous system. The comicbook was discussed during the consent process, allowing the participant to become familiar with the investigator and to understand their role in the study. Participants were encouraged to engage with the comicbook, ask questions, and familiarize themselves with the assessments. During the play component, children engaged in play-rehearsals using Playmobil® figurines, a mini-MRI scanner replica, and wheelchair toys. This playful simulation allowed them to become acquainted with the MRI protocol and the overall experience. Lastly, the practice component involved children lying in a mock scanner and practicing staying still while becoming accustomed to the typical sounds associated with MRI scans. Our participants exhibited 100% completion rate for all electrophysiology and neuroimaging assessments. Out of a total of 81 assessments, 99% of them yielded valid data. Furthermore, our participants outperformed age-matched typically developing (TD) children from the Child Mind Institute Healthy Brain Network Biobank, with a successful completion rate of 94% for MRI scans compared to 83% in the TD group. The MRI data

obtained from our participants showed significantly lower coefficients of joint variation (CJV) and entropy focus criterion (EFC), indicating reduced motion-related artifacts and improved image quality. Our child-centric approach proved effective in enhancing compliance and creating a positive research experience for children. Furthermore, our approach facilitated their understanding of the assessments, reduced intimidation, and improved familiarity with the research process and personnel. By adopting this approach, we can optimize the quality of data obtained from child participants and contribute to more successful research outcomes in the field of child neuroscience and development.

Disclosures: A.L. Behrman: None. **M.E. King:** None. **L. Alvarado:** None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.03/X4

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Feasibility of DeepLabCut technology for posture assessment in children with Spinal Cord Injury

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Abstract: Introduction: Markerless motion capture using computer vision techniques is a versatile and cost-effective method for accurate video analysis in research and clinical settings. However, the primary challenge in utilizing machine/deep learning techniques for video analysis lies in optimizing the program and its parameters to minimize errors and maximize efficiency. For custom-trained techniques like DeepLabCut for angle analysis, there are several adjustable parameters during model training for a given video, such as the number of iterations, frames, and train-test split, which significantly affect the accuracy of the results. The primary goal of this study was to investigate the feasibility of training a network on DeepLabCut and evaluate the accuracy of its 2D model compared to existing manual marking technique via MaxTRAQ software. **Methods:** Segmental trunk angles measured via DeepLabCut were compared to MaxTRAQ software. Segmental trunk angles were marked and calculated from trunk posture assessment videos, collected from 4 pediatric participants (6.5 ± 3.7 years old) with spinal cord injury (C2 - T6 range of injury), who completed a training study to improve sitting posture and trunk control. For each participant, trunk segments (Hear-Ear, Head-Shoulder, Head-C7, C7-T8, T8-L1, L1-L5) were identified and marked using retroreflective markers at different anatomical sites. Each participant was asked to maintain an upright sitting posture for 5 seconds for 3 attempts. A high-resolution camera recorded these 3 attempts. The DeepLabCut model was trained using about 35 videos with different iterations, marked frames, and train-test splits. Subsequently, all 35 videos were analyzed using the trained network, and results were compared

with those obtained from MaxTRAQ, where a trained technician manually marked the anatomical sites in the videos for segmental angle analysis. **Results:** Optimal parameters that provided the least train-test pixel error: 125,000 iterations, 15 frames per video, 95:5 train-test split, were identified. Segmental angles obtained from DeepLabCut were compared frame by frame with MaxTRAQ and Root Mean Square Error (RMSE) was calculated. The RMSE values for Head-Ear = 5.03 ± 5.24, Head-Shoulder = 1.1 ± 0.7, Head-C7 = 1.2 ± 0.9, C7-T8 = 1.6 ± 1.7, T8-L1 = 1.6 ± 2.1, L1-L5 = 3.6 ± 7.7, where a lower value translates to better accuracy by the model. **Conclusion:** Thus, preliminary data demonstrates that DeepLabCut is a feasible and accurate method of calculating segmental trunk angles in 2D space using computer vision techniques.

Disclosures: P. Parikh: None. **B. Carlsen:** None. **A. Adhikari:** None. **G. Singh:** None. **K. Lucas:** None. **A.L. Behrman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Behrman receives royalties as a co-author of a text, Locomotor Training: Principles and Practice from Oxford University Press.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.04/X5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life

Title: Combining Literature Inference Meta-analysis & Biodata Evidence Research (CLIMBER)

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Abstract: Combining Literature Inference Meta-analysis & Biodata Evidence Research (CLIMBER)
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Translation of spinal cord injury (SCI) therapeutics from preclinical animal studies into human studies is limited. To bridge this translation and better assess predictors of functional improvement (neuro-conversion), we compared published data with raw subject-level data. Methods were combined from the Collaborative Approach to Meta Analysis and Review of Animal Experimental Studies (CAMARADES) and individual participant data available in the Open Data Commons for Spinal Cord Injury (odc-sci.org). The systematic review and extraction of data from 32 published papers yielded N=1454 subjects, while individual participant data from these same papers included N=2074 subjects. The N difference may reflect publication bias, with authors frequently publishing only a subset of subjects. Meta-regression models were used to compare neuromotor outcomes in different rodent types, sex, animal strains, sample sizes, injury models, anesthetics, and outcome measures. Strain types, injury severities, behavioral measures, and anesthetic types showed notable differences in effect sizes. Meta-analysis was refined to publications with common injury models (contusive injuries) and the most standardized endpoints (open field assessments). With analysis focused on these parameters, significant differences in effect sizes were observed in strain and rodent types. Lastly, it was found that publications with the smallest sample sizes yielded the largest effect sizes and studies with the largest sample sizes had the smallest effect sizes. This indicates a potential overinflation of effect sizes by inadequately powered small studies, reflecting selection bias. Together the results demonstrate the feasibility and utility of combining individual participant data analysis and traditional literature-sourced meta-analysis to explore effect size reproducibility in SCI.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.05/X6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: the National Research Foundation (NRF) (2019R1A6A1A11034536, RS-2023-00208315)
Electronics and Telecommunications Research Institute (ETRI) grant (21YR2410)

Title: Predictive Modeling of Decubitus Ulcer Occurrence in Spinal Cord Injury Patients Using Artificial Intelligence

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Abstract: Decubitus ulcers (DUs) pose a significant challenge in the care of spinal cord injury (SCI) patients, often leading to a substantial decrease in their quality of life. Therefore, the development of effective screening methods to identify high-risk individuals for DU onset is of paramount importance. This study investigates the use of machine learning and deep learning techniques to create highly precise predictive models for DU occurrence in SCI patients. We reviewed a total of 539 SCI patients, with a 35% incidence rate of DU (189 subjects) during their hospital stay. We gathered 139 parameters, encompassing baseline characteristics, neurological, functional, and laboratory parameters. For the non-DU group, laboratory data was selected at the initial assessment time, while for the DU group, it was chosen two weeks prior to DU onset. To contrast the machine learning and deep learning models with traditional statistical methods, we employed independent t-tests, Chi-square tests, and logistic regression analysis. Various machine learning and deep learning techniques were utilized, including graph neural networks (GNN), deep neural networks (DNN), linear support vector machines (SVM_linear), support vector machines with radial basis function kernel (SVM_RBF), K-nearest neighbors (KNN), random forests (RF), and logistic regression (LR) models. These models underwent data preprocessing and feature selection, and the data was trained through cross-validation for DU classification. Our statistical analysis revealed significant differences in several neurological and functional parameters between the non-DU and DU groups. In the machine learning approach, the top 20 laboratory parameters were ranked by importance based on the RF outcome. Notably, the DNN model achieved the highest accuracy (0.870) when considering only laboratory parameters. When both laboratory and clinical parameters were combined, logistic regression displayed the highest accuracy (0.877). Decision tree classification models were created for DU prediction using the featured laboratory parameters, with the hematocrit level identified as the primary discriminator for group determination between non-DU and DU groups.In conclusion, our study indicates that ML algorithms, particularly DNN and logistic regression, show excellent performance in predicting DU. Laboratory tests, along with clinical evaluation, are significant factors in these predictions. We propose that artificial intelligence-based prediction model could be a valuable tool for the prevention and early detection of DU in SCI patients in a clinical setting.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.06/X7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS K23NS091430-03
PHF Team Science Award

Title: Detection of Motor Tract Damage and Dexterity Loss with Magnetization Transfer Ratio in Patients with Degenerative Cervical Myelopathy - a Pilot Study

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Abstract: Degenerative cervical myelopathy (DCM) is a common, non-traumatic degenerative disease in aging adults that can lead to motor and sensory disfunctions. Currently, the standard clinical diagnostic tool for DCM, the modified Japanese Orthopedic Association (mJOA) score, can qualitatively measure DCM severity by assessing peripheral nerve impairment, but cannot provide a quantitative measure. Magnetization transfer ratio (MTR) is an imaging technique that can indirectly measure white matter (WM) volumes within the spinal cord. The objective of this study is to assess MTR's ability to quantify regional and tract-specific WM damage in DCM. Magnetization transfer (MT) imaging was applied to 7 healthy controls (HCs) and 10 DCM patients using a 3T GE MRI scanner. MTR values were extracted from the range of max compression in each region and tract-specific area, identified with the Spinal Cord Toolbox (SCT) PAM50 atlases. Each subject also performed biomechanical measures of dexterity, grip strength, balance, and gait speed using the NIH Toolbox. Differences in DCM and HC MTR values were calculated using a one-tailed Mann-Whitney test. A Spearman's correlation was also applied to tract-specific MTR values and motor testing results. HC and DCM MTR values showed significant differences in the lateral regions ($p = 0.0439$), and the ventral corticospinal ($p = 0.0093$) and tectospinal ($p = 0.0215$) tracts. HC and DCM MTR values failed to show significant difference in the dorsal and ventral regions ($p = 0.1148$, $p = 0.0544$), and the lateral corticospinal ($p = 0.2087$), fasciculus cuneatus ($p = 0.0966$), fasciculus gracilis ($p = 0.1819$), ventral and lateral reticulospinal ($p = 0.0966$, $p = 0.0665$), medial fasciculus ($p = 0.0665$), rubrospinal ($p = 0.1349$), spinal lemniscus ($p = 0.0806$), spino-olivary ($p = 0.1148$), ventral spinocerebellar ($p = 0.4434$), and vestibulospinal ($p = 0.1148$) tracts. Spearman's correlation analysis revealed a significant correlation between dexterity and MTR values within the ventral corticospinal tract ($p = 0.017$, $r = 0.576$). Within the healthy human spinal cord, the corticospinal tract allows for voluntary motor control of peripheral limbs. However, damage to tract WM can result in loss of upper limb dexterity, which is a prevalent symptom within DCM patients. Our results reflect the relationship between MTR values and dexterity measures, and WM changes in corticospinal tracts of DCM patients. In this sense, tract-specific MTR values can become an important clinical diagnostic tool for the identification and treatment of DCM because it can quantitatively reflect key impairments within the WM and establish a specific origin for symptom manifestation.

Disclosures: **G. Haynes:** A. Employment/Salary (full or part-time):; University of Oklahoma. **F. Muhammad:** A. Employment/Salary (full or part-time):; University of Oklahoma Health Sciences Center. **L. Ding:** A. Employment/Salary (full or part-time):; University of Oklahoma. Other; Institute for Biomedical Engineering, Science and Technology. **Z.A. Smith:** A. Employment/Salary (full or part-time):; University of Oklahoma Health Sciences Center. 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 Institutes of Health, Presbyterian Health Foundation.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.07/X8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NYSCIRB Institutional Support

Title: Antibody levels against SARS-CoV-2 in Veterans with chronic spinal cord injury: a cross sectional analyses

Authors: D. J. MORRISON[1], E. DEMATT[2], K. JONES[2], Z. MI[2], K. BISWAS[2], M. GALEA[3,4], A. M. SPUNGEN[3,4], *O. BLOOM[1,5];
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Abstract: Veterans with chronic spinal cord injury (SCI) are often immunosuppressed and have chronic health conditions associated in the general population with higher risk of complications and more severe symptoms of COVID-19. To our knowledge, there is no public data on antibody responses to SARS-CoV-2 infection or vaccination in Veterans with SCI. In 2021, we surveyed Veterans with SCI who consented for screening in the VA Cooperative Study CS#2003 (NCT02658656) about the COVID-19 pandemic. Standard VA Core Lab assays (Abbott anti-N IgG and anti-S IgG, Beckman anti-Receptor Binding Domain "RBD") and cutoffs determined levels of anti-SARS-CoV-2 antibodies. Systemic inflammatory mediators were measured by ELISA (Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex, IBL International HMGB1 and CRP). Participants reported their clinical and demographic characteristics. There were 70 Veterans with SCI (male=91%; age=56, 11 [median, IQR] years; injury duration=11, 21 [median, IQR] years; paraplegia=76%, motor complete (AIS A or B)=47%) in the study. Few Veterans were positive for anti-N IgG (N=10), of whom most reported exposure (N=6/10) or vaccination (N=7/10). Most Veterans were positive for anti-RBD IgG (N=50/70); of whom a minority reported exposure (N=19/50) and a majority reported vaccination (N=35/50). Of Veterans who were positive for anti-RBD IgG, titers correlated significantly with anti-S and anti-N IgG (Pearson's correlation R=0.92 and 0.59, $P<1.09 \times 10^{-19}$, P<0.0000007 respectively). Most Veterans were positive for anti-S IgG (N=59/70), of whom a minority reported exposure (N=25/59) and a majority reported vaccination (N=41/59). Among Veterans who were positive for anti-S IgG, titers correlated significantly with anti-RBD and anti-N IgG (Pearson's correlation R=0.94 and 0.52, $P<5.16 \times 10^{-27}$ and P<0.00003 respectively). Most participants had a moderate or high risk of cardiovascular disease based on CRP levels (mg/L: high >3: 50%,

moderate 1-2.9: 19%, low risk <1.0: 31%). HMGB1 levels (5.3±0.7 ng/ml, mean± SEM) were in range of reported values for persons with SCI (Papatheodorou et al 2017). Chemokines IP-10, MIP-1a and MIG were elevated in anti-S IgG reactive participants; the cytokine MIF was decreased ($P<0.05$, Mann Whitney). IP-10, MIP-1a and MSCF were lower in anti-N IgG reactive participants ($P<0.05$, Mann Whitney). Veterans with SCI had measurable levels of anti-SARS-CoV-2 antibodies. As in the general population, anti-S and anti-RBD IgG levels correlated significantly. Prospective studies are needed to measure kinetics and levels of COVID-19 antibodies after exposure or vaccination.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.08/X9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: University of Colorado Anschutz - Boulder Nexus Grant
NIH National Center of Neuromodulation for Rehabiliation P2CHD086844

Title: Increases in corticospinal excitability after acute intermittent hypoxia is coupled with improvements in sensorimotor adaptation

Authors: A. BOGARD[1], T. HEMBREE[1], A. POLLET[1], L. LATTANZIO[2], I. BUARD[2], A. C. SMITH[3], *A. Q. TAN[1];
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Abstract: Restoring voluntary movement after neurological injury hinges on the ability to promote neural plasticity of motor pathways. Promising evidence suggests that breathing mild bouts of low oxygen air (i.e., acute intermittent hypoxia, AIH) enhances corticospinal drive to upper limb muscles in healthy individuals. However, it remains unclear if such changes in excitability are associated with gains in motor control. Notably, mechanistic studies from spinally injured rodents show that AIH may engage brain-derived neurotrophic factor dependent pathways that have been linked with both increases in motoneuron excitably and improvements in motor learning. Accordingly, we examined if AIH-induced gains in corticospinal excitability to the tibialis anterior muscle (TA) would parallel improvements in motor adaptation during a split-belt walking paradigm. All participants received AIH for five consecutive days, in which they breathed 15, 90-second bouts of hypoxic air (9% O2) alternated with 60 seconds of normoxic air (21% O2). We used single-pulse transcranial magnetic stimulation (TMS) to the TA at baseline and after the fifth AIH treatment to construct recruitment curves of the average

motor evoked potential (MEP) amplitude vs. stimulus intensity. Immediately after the post-AIH TMS protocol, we assessed motor learning by quantifying changes in spatiotemporal asymmetry while split-belt walking. Following repetitive AIH, we observed an increase in the maximal TA MEP amplitude, an increase in the recruitment curve slope, and a decrease in the resting motor threshold. Consistent with previous studies, we also found that participants adapted to split-belt walking by reducing step length asymmetry, double support time asymmetry, and net metabolic power. Intriguingly, changes in the maximum TA MEP amplitude and resting motor threshold after AIH were associated with decreases in double support time asymmetry, as well as reductions in metabolic cost. These preliminary results suggest that AIH may increase the gain of lower limb motor neuron excitability, leading to more economical walking coordination strategies. The correlation between excitability and motor adaptation parameters further indicates that AIH-mediated increases in corticospinal excitability may be a potential marker for improvements in motor control. Clarifying how to harness neuromodulation techniques to optimize motor learning is critical to enhance the recovery of walking after neurological injury.

Disclosures: **A. Bogard:** None. **T. Hembree:** None. **A. Pollet:** None. **L. Lattanzio:** None. **I. Buard:** None. **A.C. Smith:** None. **A.Q. Tan:** None.

Poster

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Program #/Poster #: PSTR269.09/X10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR PJT-166040

Title: Pelvic floor muscle activation patterns during exoskeleton-assisted walking in people with complete spinal cord injury

Authors: *X. ZHOU[1,2], A. M. WILLIAMS[1,2], J.-S. BLOUIN[1], T. LAM[1,2];
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Abstract: The pelvic floor muscles (PFM) are crucial for maintaining continence and a potential therapeutic target for improving urinary control after spinal cord injury (SCI). The PFM can be recruited voluntarily in isolation or co-activated with other abdominopelvic muscles. Previous researchers showed that some people with complete SCI may have preserved corticospinal pathways to the PFM, and can co-activate the PFM during maneuvers that engage the trunk muscles. In this population, trunk muscles are recruited more effectively during walking with overground exoskeletons (e.g., Ekso) than treadmill-based devices (e.g., Lokomat), raising the question of whether such greater trunk muscle activity concomitantly activates the PFM. This within-subject, cross-sectional study aims to (1) characterize the pattern of PFM activity, and (2) explore the co-activation relationship between the PFM and trunk muscles, as well as the effect

of pelvis acceleration on PFM activation, during Lokomat- and Ekso-assisted walking in people with complete SCI. We recorded bilateral surface electromyography (EMG) from the PFM, rectus abdominis (RA), erector spinae (ES), and gluteal muscles, along with pelvis accelerometry data, during walking in the Lokomat and Ekso at 1km/h for >60 strides. Prior to the walking trials, participants performed attempted maximum voluntary contractions of each muscle for EMG normalization. We calculated an average profile of muscle activity and 3D pelvis acceleration magnitude across the gait cycle (defined as time between successive right heel strikes). In controls, PFM EMG amplitude was 88±31% higher during walking in the Ekso than Lokomat. Greater PFM activation was observed alongside higher EMG amplitude from the RA, ES, and gluteal muscles, and positively associated with pelvis acceleration ($r=0.84$, $p<0.05$). We have preliminary data from 3 male SCI participants (41±2 years old, injury level T1-T5, 2 AIS-A and 1 AIS-B) so far. Although the SCI participants could not elicit any PFM activity during attempted maximum voluntary contraction trials, their PFM were recruited during exoskeleton-assisted walking. Compared to the Lokomat, Ekso-assisted walking elicited slightly more (11±4%) PFM activity and higher pelvis acceleration (0.94±0.14g vs. 0.15±0.02g). We also observed bursts of PFM EMG coinciding with single-leg support phase; EMG activation from the other muscles was inconsistent. Results from this study suggest that the PFM can be recruited during exoskeleton-assisted walking, opening the possibility for using this type of gait therapy to recruit the PFM and exploring its potential impact on urinary function in people with SCI.

Disclosures: **X. Zhou:** None. **A.M. Williams:** None. **J. Blouin:** None. **T. Lam:** None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

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Program #/Poster #: PSTR269.10/X11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR PJT-186171

Title: Acute effects of single session pelvic floor muscle training on somatosensory and corticospinal excitability

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Abstract: The recovery of bladder function is among the top recovery priorities for people with spinal cord injury (SCI). Urogenital dysfunction, including urinary incontinence is a debilitating condition that affects up to 80% of individuals with SCI. The pelvic floor muscles (PFM), the muscles that form the base of our abdominopelvic cavity, play a critical role in urogenital functions, including maintaining urinary continence. Pelvic floor muscle training (PFMT) is commonly prescribed in non-neurological populations as a rehabilitation intervention to manage

urinary incontinence. PFMT involves practicing voluntary PFM contractions of varying intensities and durations. As a non-invasive intervention with few to no side effects, PFMT offers an attractive option for the management of urinary incontinence in neurological populations. However, we still do not have a clear understanding of the underlying neurophysiological effects of PFMT. Therefore, the objective of this study was to investigate the acute neurophysiological changes in sensorimotor pathways following a single session of PFMT, compared to a control intervention (biceps brachii contractions). We randomly assigned participants to either the experimental (PFMT) or control (biceps brachii; BB) group. Participants completed a training program consisting of 55 contractions to different intensities and durations in either their PFM or BB. To examine changes in somatosensory excitability associated with the PFM, we used electroencephalography to record somatosensory evoked potentials in response to pudendal nerve stimulation. To examine changes in corticospinal excitability, we used surface electromyography to record motor evoked potentials from the PFM elicited by transcranial magnetic stimulation over the primary motor cortex. All measures were recorded before and after a single session of training and compared between groups. Preliminary data show a trend of facilitation in somatosensory processing to the cortex following a single session of PFMT and not the control exercise, as indicated by an increase in P40 amplitude. There was no apparent change in corticospinal excitability of the PFM although participants in the PFMT group improved their performance of PFM contractions. These results suggest the acute neurophysiological effects of a short, single session of PFMT are limited to somatosensory pathways. Additional training time may be required to modulate corticospinal excitability. Understanding of the acute neurophysiological effects following a single session of PFMT will support the translation of this intervention to individuals with SCI.

Disclosures: Y. Lin: None. **A.M. Williams:** None. **T. Lam:** None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH/NINDS R01NS103481 to GMS
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Title: Enhancing rehabilitation effectiveness with coactivation of corticospinal neurons

Authors: *G. SMITH, R. SMIT, T. CAMPION, G. KOMA, M. A. LEMAY, A. SPENCE; Temple Univ., Philadelphia, PA

Abstract: Spinal Cord Injury (SCI) causes interruption of both ascending and descending spinal tracts. Unlike the peripheral nervous system, the central nervous system (CNS) does not

demonstrate significant regeneration. Research in young rodents indicates that the superior recovery, which ceases abruptly beyond postnatal day 10, is owed to the more robust regeneration of corticospinal neurons (CST) across the injury site. Here, we enhanced recovery beyond the critical age using chemogenetic modulation of higher order pathways during unstructured rehabilitation (play). At postnatal day 5 (p5) rats received intracranial (motor cortex) injection of either non-Cre-dependent excitatory DREADD (AAV2-hM3Dq), non-Cre-dependent inhibitory DREADD (AAV2-hM4Di), or control fluorescent (AAV2-GFP). At p14, all animals underwent right C5 hemisections. Subsequently, the activation of either excitatory or inhibitory DREADDs was achieved by treating diet gel with clozapine-N-oxide for 30 days at night during active play (4 randomized juvenile rats housed together). Behavioral assays consisted of IBB, grooming, cylinder touch, and grid walk, starting 10 days after removal of CNO treatment. The excitatory animals performed significantly better on all behavior assessments when compared to both the control and inhibitory cohorts. We also observed a hierarchal recovery in forelimb kinematics and electrophysiological activity where increased activation of cortical motor neurons showed the best recovery. Specifically, we found that activation of corticospinal neurons significantly improved kinematic reach distance, such that it was not significantly different from naïve animals. Due to the size of the injury and histological assessment, recovery was mediated by adaptive sprouting. Interestingly, medullary sections demonstrated significantly more post-synaptic activity in the reticulospinal tracts compared to the other groups. The excitatory group demonstrated robust interhemispheric cortical connectivity to CST neurons and contralateral sprouting of the intact CST distal the spinal cord lesion site when compared to the control and inhibitory groups. We hypothesize that cortical activity modulates axonal sprouting of the CST, while rehabilitation shapes the connects to promote recovery of function.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

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Program #/Poster #: PSTR269.12/X13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 5 T32 GM146700

Title: The Effects of Body Weight Supported Treadmill and Overground Training on the BDNF, TrkB and CREB Pathway in Severely Spinally Contused Rodents.

Authors: *J. ARAIZA[1], O. ZARAGOZA RODRIGUEZ[1], O. M. SURYAVANSHI[1], J. ZHOU[3], S. GUERRA[1], P. SANDOVAL[1], E. ALDANA[1], C. WANG[2], R. DE LEON[3], M. S. JOSEPH[3]; [2]Electrical and Computer Engin., [1]California State University, Los Angeles, Los Angeles, CA; [3]Dept. of Kinesiology, California State Univ. Los Angeles, Los Angeles, CA

Abstract: As a form of rehabilitation, exercise enhances locomotion in spinally contused animals through repeated bouts of training. Exercise strategies such as the body weight supported treadmill trainer (BWSTT) and the overground training system: circular bodyweight-supported ambulatory rodent trainers (cBART), have improved locomotion in rats. The cBART is novel rehabilitation device designed to support a percentage of a rat's body weight on an arm lever hinged on a fulcrum, allowing the animal to step volitionally while the arm rotates around the central axis. However, the molecular plasticity mechanism in the spinal cord after training is not well understood. In this study, we use severe, mid-thoracic (T7-T9) contusion spinal cord injured rodents to investigate the effects of eight weeks of training on CREB, BDNF, and TrkB, markers of plasticity. Preliminary kinematic gait analysis suggests that combined training on contused animals had altered the expression of CREB at the injury site. BDNF expression in the entire lumbar segment below the contusion site was greater in the contused BWSTT group compared to the combined group. Significant differences in TrkB expression between groups for each spinal segment were not observed. These results suggest that in this severe contusion injury model, the combined training modulates the expression of select plasticity markers differently compared to treadmill training alone in severely contused rats, likely from activating both volitional and reflexive pathways. Additional analysis will be required to examine the locomotor behavior to confirm the relation to CREB, BDNF, and TrkB expression in the trained and control groups. Ultimately, a better understanding of training and plasticity will facilitate efforts to restore neuromotor function after a spinal cord injury or in other debilitating conditions.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

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Program #/Poster #: PSTR269.13/X14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Dr. Joseph RISCA Cal State LA 2021-2022 Mini Grant
NIH U-URISE T34GM145503
Bridges to the Doctorate 5T23GM146700

Title: Exercised induced plasticity of AADC and 5HT synthesis in spinal cord contused rodent

Authors: *E. ALDANA, S. GUERRA, J. ARAIZA, J. ZHOU, O. ZARAGOZA RODRIGUEZ, P. SANDOVAL, Y. WANG, M. S. JOSEPH;
California State University, Los Angeles, Los Angeles, CA

Abstract: Spinal cord injury (SCI) affects many lives and development of therapeutic strategies is critical to improve patient lives. Exercise training as an intervention for SCI animals and

human patients have shown many gains in locomotor improvement. Exercise training strategies such as the body weight supported treadmill trainer (BWSTT) and the over ground training system, circular bodyweight-supported ambulatory rodent trainers, individually have been shown to improve locomotion in rodents. The mechanism of plasticity is not well understood. Following SCI, the serotonin levels decrease in the spinal cord. Serotonergic activation with exercise has been shown to facilitate locomotor recovery. This study examined the relationship of exercise and the potential plasticity in the *de novo* synthesis in the spinal cord of midthoracic (T7-T9) severe contused rodents. Moreover, cells found around the central channel, C2, T4, L2, and L5 dorsal horn regions of the spinal cord have been associated with synthesizing serotonin. This study examined the exercised mediates plasticity on *de novo* serotonin production in the thoracic injury site, and the lumbar segments of the spinal cord. Brain-derived neurotrophic factor (BDNF) is another marker that plays a significant role in neuronal growth and assists in neuronal plasticity. We investigated expressions of the DDC, 5HT-2a receptor and BDNF spinal cord and how exercises intervention can affect levels of 5-HT 2a receptor, BDNF and DDC. Preliminary analysis suggests the data suggests, in this severe midthoracic contused model the DDC expression increased in the L3-L5 segments in the over ground cBART training when compared to the contused untrained rats. As shown in other studies, 5HT-2a Receptors decreased expression the lumbar segment when compared. We hope to better understand the mechanism of the serotonergic pathway to help potentially develop training and pharmacological strategies to facilitate recovery after spinal cord injury in patients.

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Poster

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Program #/Poster #: PSTR269.14/X15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01NS121336

Title: Exercise improves cardiac autonomic regulation to alleviate arrhythmias in rats with spinal cord injury

Authors: M. CUSIMANO, E. TAUB, E. OATMAN, A. SINGH, J. HOULE, *S. HOU; Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: High-level spinal cord injuries (SCI) disrupt supraspinal regulation of cardiovascular sympathetic activity, resulting in disordered hemodynamics and cardio-electric conduction. Previous studies have demonstrated that exercise after SCI promotes central neuronal plasticity and prevents peripheral organ atrophy for bodily functional recovery, such as blood pressure and heart rate. Here, we examined whether exercise training following SCI augments the balance of

cardiac autonomic activity to alleviate arrhythmias. Rats received a complete crush at the 2nd/3rd thoracic (T2/3) spinal cord level. Subsequently, passive hindlimb cycling (PHLC) was initiated and continued for 5 or 10 weeks. Rats receiving SCI without exercise and naïve ones served as controls. Afterwards, a telemetric transmitter was implanted into abdominal cavity to record blood pressure and electrocardiography (ECG), including 1) 24-h resting recordings, 2) colorectal distention (CRD)-induced autonomic dysreflexia, 3) dobutamine (DOB) stress tests, and 4) pharmacological interventions for sympathetic and parasympathetic tone. As a result, exercise regardless of duration reduced aberrant high cardiac parasympathetic tone and improved autonomic homeostasis. Though cycling training did not influence resting hemodynamics and the severity of CRD-induced autonomic dysreflexia, it reduced the number of spontaneous autonomic dysreflexia events over a 24-h period. Notably, exercise attenuated, at different extents, the occurrence of arrhythmias triggered by CRD or DOB, which was more prominent in the group with 10-week continuous training, particularly in severe rhythmic problems, e.g., A-V block, premature ventricular contractions, and sinus pause. Together, the results suggest that activity-based training enhances autonomic balance to improve cardiac electrical conduction following SCI.

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Poster

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Department of Defense Grant W81XWH-18-1-0675
Kentucky Spinal Cord and Head Injury Research Trust Grant 17-5

Title: Impact of activity-based training duration on bowel function in a rat model of spinal cord injury

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[1]Univ. of Louisville Anatom. Sci. & Neurobio., Louisville, KY; [2]Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY

Abstract: Significant bowel-related issues after spinal cord injury (SCI) that affect morbidity and quality of life include diminished bowel motility, loss of sphincter control, gastric ulcers, autonomic dysreflexia, pain, diarrhea, constipation, and fecal incontinence. Diagnoses and research in humans have largely relied on anorectal manometry (ARM) procedures to increase understanding of the functional effects of SCI on colorectal motility and defecation physiology. Recent pre-clinical rodent studies have also used ARM to further our understanding of bowel-related dysfunctions post-SCI. In the present study, the benefits of different activity-based

training (ABT) regimens on bowel function were examined. Six groups of male rats including two non-trained (uninjured and SCI) and four ABT (quadrupedal stepping on a treadmill) groups. All ABT animals received four weeks of one-hour daily stepping beginning two-weeks post SCI followed by variable amounts for four additional weeks (none; daily; once a week; daily for final 4th week only). Outcome measures included fecal output (home cage; metabolic cage) throughout the study and terminal measurements (post 8-weeks ABT) of external anal sphincter electromyography, resting anorectal pressure, and giant contraction activation under urethane anesthesia. The results indicate that treadmill training normalized defecation amount based on feces weight and food intake, as well as giant contraction frequency, external anal sphincter latency and amplitude during fecal expulsion, and resting pressure in specific areas within the colorectum. The two intermittent training groups consistently showed recorded metrics comparable to the non-injured group. The results demonstrate bowel dysfunction in the rodent SCI contusion model with improvements in functional outcomes following ABT. Importantly, the benefits to bowel-related functions with versus without intermittent ABT illustrates the need for periodic therapy to maintain the functional gains of ABT.

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Poster

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Program #/Poster #: PSTR269.16/X17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Nielsen Foundation SCIRTS Pilot Grant

Title: Effect of high-low training on well-being after chronic spinal cord injury

Authors: *C. M. J. STUART[1], D. R. S. BRITSCH[2], K. M. COTTER[2], J. TURCHAN-CHOLEWO[2], W. J. ALILAIN[3], A. M. STOWE[4];
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Abstract: Introduction: Athletes utilize high-low training (H-L) to maximize athletic performance by exercising under normoxic conditions paired with hypoxic exposure when not exercising. Individually, exercise and hypoxia are beneficial in treating spinal cord injury (SCI) in rodent models. Exercise after SCI increases neurotrophins whose decreased levels are associated with anxiety-like behavior. In humans with SCI, decreased well-being is attributed to increased rates of mental disorders and suicide. Chronic SCI is prevalent as only 0.6 % of patients fully recover and 30% of patients are rehospitalized within any given year due to

diseases of the skin, circulatory, and musculoskeletal systems. Post-SCI inflammation is common and linked with increased anxiety-like behavior. One aspect of this project was to test the hypothesis that H-L training doesn't induce anxiety when implemented chronically after SCI. H-L training was executed in rats with chronic SCI by combining voluntary overnight exercise with repetitive, sustained hypoxia 5 days a week for 8 weeks. **Methods:** Starting with n=62, and final n=49, Sprague Dawley female rats underwent baseline training before receiving a left C2 hemisection (LC2Hx). Subjects were randomly assigned to 4 groups: sedentary control, H-L, exercise-only, or hypoxia-only. At 6-7 weeks post-injury (WPI) treatment was initiated. Voluntary exercise was performed via exercise wheel access overnight and sustained repetitive hypoxia was administered in 4-hour bouts of 11% oxygen exposure. At 5, 9, and 13 WPI, Activity Boxes were used to measure anxiety-like behavior. Following LC2Hx, weights were checked weekly.**Results:** All H-L rats exercised voluntarily. Monitored exercise wheels showed that H-L subjects tend to increase voluntary exercise distance and speed over time. There was an increase in total distance run in the Activity Box for H-L rats before treatment and 8 weeks after starting treatment (p=0.0064). Activity Box data showed that after 4 weeks of treatment, H-L rats had increased (p =0.0126) rearing activity compared to sedentary rats. Sedentary rats increased time spent in the perimeter (open field assay) at each timepoint (p=0.0024), while H-L rats experienced an insignificant negative trend in time spent in perimeter. Weekly weight checks showed an expected decrease in all subjects, but both groups gained weight as the experiment progressed.**Conclusions:** While experiments with the hypoxia-only and exercise-only controls are ongoing, H-L was tolerated by rats with chronic SCI and shows potential as a treatment for humans with SCI without unnecessarily increasing post-SCI anxiety.

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Poster

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Program #/Poster #: PSTR269.17/X18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Nielsen SCIRTS Pilot Grant 727572

Title: High-low training as a rehabilitative therapy for chronic spinal cord injury

Authors: *D. BRITSCH[1], K. COTTER[2], B. ROSE[3], C. STUART[3], M. MALONE[2], T. UJAS[2], J. TURCHAN-CHOLEWO[4], W. ALILAIN[2], A. STOWE[4];
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Abstract: Objectives: The technique of "living High, training Low" (H-L) is used by athletes to improve exercise performance. H-L involves repeated cycles of exercise performed at normoxic conditions coupled with hypoxic exposure during periods of rest. Exercise and hypoxia can

individually promote recovery in CNS injury. Rodent models of spinal cord injury (SCI) implementing exercise after injury often show improved recovery of locomotion, while application of hypoxia can induce respiratory motor plasticity to promote recovery. Respiratory disease is a leading cause of rehospitalization and death for people who survive the first 24 hours after SCI. Additionally, less than 1% of human patients regain pre-injury motor function. This project tests the hypothesis that H-L training - initiated as a chronic SCI therapy - is tolerable and improves respiratory, locomotor and sensory function over time. Methods: 62 S.D. rats (F, 3-4 mo.) received a left C2 hemisection, with n=49 surviving to group allocation. Pair-housed cages were randomly assigned to H-L, hypoxia-only, exercise-only, or control group. Treatment began 6-7 weeks post-injury (WPI) and lasted for 8 weeks. H-L treatment was implemented by combining cycles of voluntary exercise with repeated administration of moderate, sustained hypoxia. For 5 days a week, H-L and exercise subjects were housed individually in cages with monitored exercise wheels overnight, and then returned to pair-housed cages in the morning. Sedentary subjects were individually housed overnight on the same schedule as exercise subjects without access to wheels. Immediately following return to pair housing, the H-L and hypoxia groups received 4 hours of 11% O_2. Motor assays (Catwalk, whole body plethysmography, Activity Box) and blood draws were performed at baseline, 5 WPI, 9 WPI and 13 WPI. A sensory assay (Hargreaves) was also performed at 13 WPI. At 14 WPI subjects underwent a terminal, bilateral diaphragm EMG to assess activity. Multiple tissues were collected for histology and cell profiling. Conclusions: 2 cohorts are still ongoing. MATLAB is being optimized for EMG analysis. Most notably, the H-L group experienced decreased frequency (2way RM ANOVA p=0.004) and increased tidal volume (2way RM ANOVA p=0.005) between pre-treatment and 4 weeks later, while control subjects did not, indicating improved respiratory function. H-L group also presented a promising but nonsignificant trend towards reduced hyperalgesia in the contralateral hindpaw compared to control group. Preliminary analysis shows treatment was well-tolerated in chronic SCI rats and has high translational potential.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.18/X19

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation

Title: Gamified Electromyographic Biofeedback with Wearable Sensors is Enjoyable for People with Tetraplegia and Promotes Large Dosages

Authors: *R. COTTON;
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Abstract: People with tetraplegia consistently rank recovery of arm function among their highest priorities to improve independence and quality of life. Intensive, repetitive practice can stimulate motor recovery through activity-dependent plasticity and generally produces a greater benefit with greater dosage, but we lack the tools to help patients perform enough high-quality practice at home. To address this gap, we developed a wearable, Bluetooth-connected electromyography (EMG) sensor platform with smartphone games to enable people with spinal cord injury (SCI) to perform EMG biofeedback.

We tested this system on people with acute tetraplegia seen during inpatient rehabilitation. We able to successfully perform EMG biofeedback on numerous paretic muscles, including wrist extensors, wrist pronators, triceps, biceps, and deltoids, although in some cases muscle activity was insufficient for successful control. We assessed engagement with the games using the Physical Activity Enjoyment Scale (PACES). Most participants rated both games as highly enjoyable and on average preferred a game that required more varied muscle activity. However, this game also typically promoted lower maximum intensity muscle activity compared to one that repeatedly requests a maximum activation. In each one-hour treatment sessions, most commonly involving four muscles, participants typically performed hundred to thousands of repetitions.

We also tested this system in multiple sessions over a month on participants with chronic tetraplegia. Like sessions during inpatient, participants continued to perform large repetition dosages throughout the protocol and continued to find the games enjoyable. Participants also gave anecdotal reports of functional improvements. One participant reported improvements in finger extension, one with improvements in triceps activation and wrist pronation, and another with improved ability to reach across the body and perform bilateral tasks.

People with tetraplegia find gamified electromyographic therapy provided via wearable sensors enjoyable and achieved large therapeutic dosages when playing it. Of our two games, the one that participants on average most prefer produces smaller maximal muscle activations, and future work is required to optimize and balance these two tradeoffs. Our initial results also indicate it can produce functional improvements over multiple sessions. Ongoing studies will provide further evidence of efficacy and to test the ability to perform this as home therapy.

Acknowledgments This work was generously supported by the Craig H. Neilsen Foundation and the Shirley Ryan AbilityLab research accelerator.

Disclosures: R. Cotton: None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.19/X20

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Enhancing corticospinal-motoneuronal plasticity by 4-aminopyridine in humans with spinal cord injury: a phase 2b clinical trial

Authors: B. CHEN[1,2], *M. PEREZ[1,3,4,2];
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Abstract: Paired corticospinal-motoneuronal stimulation (PCMS) has been shown to promote functional recovery in humans with spinal cord injury (SCI). The goal of our study was to assess the effect of 4-aminopyridine (4-AP), a nonselective blocker of voltage-sensitive potassium channels, on PCMS induced plasticity in humans with chronic SCI. Participants with chronic SCI were randomly assigned to receive 40-sessions of PCMS targeting corticospinal-motoneuronal synapses of multiple leg muscles followed by exercise combined with 10 mg of 4-aminopyridine (4-AP, also known as dalfampridine) or 10 mg of a placebo tablet. During PCMS, 180 paired pulses elicited corticospinal action potentials by electrical stimulation (thoracic spine) allowing volleys to arrive at the spinal cord 1-2 milliseconds before motoneurons were activated retrogradely via bilateral electrical stimulation (femoral nerve, common peroneal nerve, and posterior tibial nerve) for quadriceps femoris, tibialis anterior, and soleus muscles. We measured motor evoked potentials (MEPs) and maximal voluntary contractions in all muscles targeted as well as the 10-min and 6-min walk test before and after the repeated sessions in both groups. We found that MEP size and maximal voluntary contractions in all muscles targeted increased after 20 sessions and further increased after 40 sessions but to a larger extent in participants that received 4-AP compared to the group that received placebo. Notably, in people in the 4-AP group, walking speed (measured by the 10-meter walk test) and endurance (measured by the 6-minute walk test) largely enhanced after 20 sessions and further improved after 40 sessions compared with baseline. Our results demonstrate that combinatorial approaches using neurostimulation and 4-AP represent an avenue to further enhance functional restoration following chronic SCI.

Disclosures: B. Chen: None. **M. Perez:** None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.20/X21

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Paired corticospinal-motoneuronal plasticity to target respiratory function in humans with spinal cord injury

Authors: *B. CHEN[1,2], M. PEREZ[1,3,4,2];
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Physical Med. and Rehabil., [4]Dept. of Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL

Abstract: Respiratory function is often impaired in individuals with high cervical spinal cord injury (SCI, C3-C5), leading to reduced quality of life and mortality. Respiratory complications developed in these individuals are largely related to diaphragm impairment. Paired corticospinal-motoneuronal stimulation (PCMS), a noninvasive neurostimulation protocol based on principle of spike-timing dependent plasticity (STDP), effectively promotes recovery in upper- and lower-limb muscles in humans with SCI. Here, we examined the effect of PCMS in the diaphragm muscle in control subjects and in individuals with high cervical chronic SCI. During PCMS, corticospinal volleys evoked by transcranial magnetic stimulation (TMS) over the leg motor cortex were timed to arrive at corticospinal-motoneuronal synapses of the diaphragm muscle 1-2 ms before the arrival of antidromic potentials elicited in motoneurons by electrical stimulation of the phrenic nerve. We tested motor evoked potentials (MEPs) elicited by TMS over the leg motor cortex in the diaphragm muscle before and after 180 paired-pulses. Respiratory function was measured before and after paired-pulses in individuals with SCI. We found that MEP size at rest and electromyograpic activity in the diaphragm during maximal inspiratory effort increased after a single session of PCMS in controls and SCI participants. A ventilator-dependent participant underwent 40 sessions of PCMS combined with standard physical therapy. Notably, we found that vital capacity, forced vital capacity, forced expiratory volume, and maximal voluntary ventilation improved after repeated sessions compared with baseline measures. These results suggest that STDP-like plasticity can represent an avenue to enhance respiratory function following high cervical SCI.

Disclosures: B. Chen: None. **M. Perez:** None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.21/X22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS
VA
NIH Grant HD07418

Title: Differential Effect of Corticospinal-Motoneuronal Plasticity in Elbow Flexor and Extensor Muscles in Humans with Spinal Cord Injury

Authors: *C. L. P. BUTLER[1,2,3,4], M. A. PEREZ[1,3,4];
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Abstract: Individuals with cervical spinal cord injury (SCI) exhibit limited motor recovery in elbow extensors compared to elbow flexor muscles. The goal of our study was to assess the effect of paired corticospinal-motoneuronal stimulation (PCMS) on corticospinal excitability in elbow flexor and extensor muscles in humans with and without spinal cord injury (SCI). During PCMS, corticospinal volleys evoked by transcranial magnetic stimulation (TMS) were timed precisely to arrive at corticospinal-motoneuronal synapses of the biceps and triceps brachii muscles 1-2 ms prior to the arrival of antidromic potentials elicited through electrical stimulation of the musculocutaneous and radial nerves at the brachial plexus. The interstimulus interval (ISI) between TMS and peripheral nerve stimulation [calculated by using the latency of motor evoked potentials (MEPs), C-roots, and maximal motor responses], was similar between muscles in control (biceps=4.0±1.0ms, triceps=4.1±0.7ms; p=0.8; n=7) and SCI (biceps=4.1±5.1ms, triceps=4.2±5.8ms; p=0.9; n=3) participants. Thus, PCMS was used to target both muscles concurrently using suprathreshold stimulation. We tested the effect of PCMS on MEPs elicited by TMS over the arm representation of the motor cortex in biceps and triceps brachii before and after 180 paired pulses in humans with and without chronic cervical SCI. We found that MEP size increased after PCMS in the biceps brachii to a larger extent than in the triceps brachii in control (biceps=194.4±114.2% of baseline, triceps=124.8±71.4% of baseline) and SCI (biceps=528.0±214.1% of baseline, triceps=137.8±62.2% of baseline) participants. Our findings suggest that in humans spike-timing dependent plasticity mechanisms are easily engaged in elbow flexors compared to elbow extensors muscles. This knowledge might contribute to the design of targeted strategies aiming to enhance upper limb function after SCI.

Disclosures: C.L.P. Butler: None. **M.A. Perez:** None.

Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.22/X23

Topic: C.11. Spinal Cord Injury and Plasticity

Support: National Institute of Neurological Disorders and Stroke
Department of Veterans Affairs
Craig H. Neilsen Foundation

Title: Spasticity predicts motor recovery for patients with subacute motor complete spinal cord injury

Authors: *S. SANGARI[1], B. CHEN[1], F. GROVER[1], H. SALSABILI[1], M. SHETH[1], K. GOHIL[1], S. HOBBS[1], A. OLSON[1], A. ANSCHEL[1,2], K. KIM[1,2], D. CHEN[1,2], A. KESSLER[1,2], M. OUDEGA[1,2,3], B. K. KWON[4], S. KIRSHBLUM[5], J. D. GUEST[6], M. A. PEREZ[1,2,3]; [1]Shirley Ryan AbilityLab, Chicago, IL; [2]Northwestern Univ., Chicago, IL; [3]Edward Hines Jr. VA Hosp., Hines, IL; [4]Univ. of British Columbia, ICORD, UBC, Vancouver, BC, Canada;

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Abstract: A motor complete spinal cord injury (SCI) results in the loss of voluntary motor control below the point of injury. Some of these patients can regain partial motor function through inpatient rehabilitation; however, there is currently no biomarker to easily identify which patients have this potential. Existing research indicates that spasticity could be that marker. It was found that patients with motor complete SCI who exhibit spasticity show preservation of descending motor pathways, the pathways necessary for motor signals to be carried from the brain to the target muscle. We hypothesized that the presence of spasticity predicts motor recovery after subacute motor complete SCI. Spasticity and descending connectivity were tested in the quadriceps femoris muscle in patients with subacute motor complete (n=36) and motor incomplete (n=30) SCI. Neurological recovery was assessed by using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and the American Spinal Injury Association Impairment Scale (AIS). All measurements were taken at admission and discharge from inpatient rehabilitation. We found that motor complete SCI patients with spasticity improved in motor scores and showed AIS conversion to either motor or sensory incomplete. Conversely, patients without spasticity showed no changes in motor scores and AIS conversion. In incomplete SCI patients, motor scores improved and AIS conversion occurred regardless of spasticity. These findings indicate that spasticity represents an easy-to-use physiological biomarker to predict motor recovery after severe SCI. This knowledge can improve the effectiveness of inpatient rehabilitation for complete SCI patients.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.23/X24

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Post-activation depression is attenuated in humans with spinal cord injury with and without spasticity

Authors: *M. NITO[1,2,3], B. CHEN[1,2,4], J. B. NIELSEN[5], M. A. PEREZ[1,2,4];
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Abstract: Post-activation depression (PAD) is thought to be one of the mechanisms altered after spinal cord injury (SCI) that might contribute to spasticity. However, limited information is available on how PAD differs between humans with SCI with and without spasticity. To address this question, we tested the soleus H-reflex at interstimulus intervals of 1, 2, 4, and 10 s using half of the maximal H-reflex (half H-max) and the maximal H-reflex (H-max) size in 34 individuals with chronic (≥6 month) SCI and 17 aged-matched control subjects. Spasticity in the soleus muscle was assessed by the stretch reflex (elicited by rapid >300°/s passive dorsiflexion of the ankle) and the Modified Ashworth Scale (MAS). The presence or absence of spasticity in individuals with SCI was classified based on the highest amplitude of stretch reflex obtained in control subjects. We found that the H-max was similar in individuals with SCI with and without spasticity and control subjects, whereas the M-max was smaller in both groups of individuals with SCI compared with control subjects. PAD was stronger at shorter interstimulus intervals at half H-max compared with H-max in individuals with SCI with and without spasticity and control subjects. Notably, PAD was attenuated to a lesser extent in individuals with SCI compared with control subjects but no differences were found in individuals with SCI with and without spasticity. In addition, the magnitude of PAD was not correlated with the stretch reflex and the MAS. Our findings demonstrate that PAD is attenuated following SCI regardless of the presence of spasticity, suggesting that it is less likely that PAD plays a role in the pathophysiology of spasticity.

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Poster

PSTR269. Spinal Cord Injury: Clinical Perspectives and Rehabilitation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.24/X25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Foundation Grant 647662
CDMRP W81XWH1810718

Title: Spinal cord injury changes the relationship of ventilatory drive to breathing

Authors: *T. SUTOR[1], M. MIR[2], J. WELCH[5], A. VOSE[2], G. S. MITCHELL[3], E. J. FOX[4]; [1]Univ. of Florida, GAINESVILLE, FL; [3]Univ. of Florida, [2]Univ. of Florida, Gainesville, FL; [4]Brooks Rehabil., Univ. of Florida, Jacksonville, FL; [5]Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Spinal cord injury (SCI) disrupts neural pathways necessary to breathe. Resting ventilatory drive measured by mouth pressure 0.1 seconds after an unexpected inspiratory occlusion (P0.1) is elevated in persons with acute (<6 months) SCI who are ventilator dependent. Most persons with chronic SCI breathe independently, and P0.1 is similar to non-injured (NI) persons. However, other breathing impairments persist and vary with injury severity. While P0.1

is a useful index of breathing function, P0.1 associations with injury characteristics and other breathing outcomes have not been established post-SCI. Thus, we quantified relationships between P0.1 and: 1) SCI injury characteristics; and 2) standard clinical breathing outcomes. 22 community-dwelling adults >1-year post- complete or incomplete SCI (C1-T6) enrolled in an ongoing IRB-approved trial to improve breathing were included. Retrospective data from 17 NI controls were used for comparison. P0.1, tidal volume (VT), breathing frequency (Fb) and minute ventilation (VE) at rest were collected. Neurologic level of injury (NLI), ASIA impairment scale (AIS), and time post-injury were recorded in participants. Differences between groups were compared via t-tests. Relationships between P0.1 and other variables were assessed via linear or quadratic univariate or multivariate relationships. P0.1 was not associated with NLI, AIS or time post-injury in participants with SCI, either independently or in multiple regressions. There was no difference between groups in P0.1 (NI: 1.28 cmH2O ± 0.7; SCI: 1.11 ± 0.5, $p>.05$) or Fb (NI: 14 ± 3.5 breaths/minute; SCI 13.4 ± 2.9, $p>.05$). There were significant differences in VT (NI: 0.75 ± 0.2 liters; SCI 0.6 ± 0.13, $p<.01$) and VE (NI: 10 ± 1.5 liters/minute; SCI 7.8 ± 1.4, $p<.001$). VE and P0.1 associations were linear and significant in both groups (NI: $r^2 = .24$, $p<.05$; SCI: $r^2 = .24$, $p<.05$). VT and P0.1 were quadratically associated in NI ($r^2 = .56$, $p<.01$), but unrelated in SCI. Fb and P0.1 associations were quadratic in NI ($r^2 = .69$, $p<.001$) and linear in SCI ($r^2 = .19$, $p<.05$). The lack of association between P0.1 and chosen SCI characteristics is possibly because clinical characteristics commonly used to characterize SCI do not consider ventilatory drive. While P0.1 is associated with VE at rest after SCI, changes in ventilatory drive may more likely manifest as increased Fb since impaired breathing muscle function might impair increases in VT, causing a lack of association between P0.1 and VT. These factors should be considered to provide more comprehensive insight when interpreting changes in P0.1 across time or due to interventions intended to improve breathing in this population.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.01/Y1

Topic: D.02. Somatosensation – Pain

Support: NIH Grant U19NS130607
American Heart Association Predoctoral Fellowship 828671

Title: Pain-associated differences in the intrinsic excitability of human sensory neurons

Authors: *J. YI[1], L. YANG[3], A. J. WIDMAN[2], Z. BERTELS[4], J. DEL ROSARIO[4], R. SLIVICKI[5], M. PAYNE[1], B. A. COPITS[6], R. W. GEREAU, IV[7];
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Abstract: Many preclinical studies in rodents have shown that sensory neurons in the dorsal root ganglia (DRG) exhibit heterogeneity in their intrinsic excitability that parallels their functional diversity. Changes in the intrinsic excitability of rodent DRG neurons, particularly the nociceptor subpopulation, are thought to contribute to pathogenesis and maintenance of pain; however, whether this occurs in the sensory neurons of humans with chronic pain conditions is only beginning to be explored. In this study, we examine whether the intrinsic excitability of human sensory neurons is dynamically modulated by pain history. Using DRG neurons obtained postmortem from organ donors, we have identified at least three physiologically distinct clusters of human DRG neurons that differ in their spike firing patterns, action potential kinetics, and membrane properties. By employing a "Patch-Seq" approach, we map the electrophysiologically-defined clusters to specific, transcriptionally determined subpopulations of sensory neurons. Finally, a comparison of human DRGs from donors with and without pain history reveals cluster-specific, pain history-associated differences in the intrinsic excitability and spike kinetics of human DRG neurons, as well as in the expression of voltage-gated sodium channels. Together, our results are consistent with the notion that sensory neurons from donors with pain history exhibit distinct electrophysiological profiles compared to DRG neurons from donors without pain history.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.02/Web Only

Topic: D.02. Somatosensation – Pain

Title: Peripheral antinociception induced by carvacrol: Activation of the opioid receptor-Nitric Oxide-cGMP-potassium channel pathway

Authors: *M. I. ORTIZ[1], G. CASTAÑEDA-HERNÁNDEZ[2];
[1]Área Académica De Medicina, ICSA, UAEH, Pachuca de Soto, Mexico; [2]Dept. de Farmacología, Ctr. de Investigación y de Estudios Avanzados del Inst. Politécnico Nacional, Cd. México, Mexico

Abstract: The aim of this study was to examine if the local antinociception of carvacrol comprise the participation of a biguanide-dependent mechanism and the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)-K^+ channel pathway in the 1% formalin test. Male Wistar rats were injected in the dorsal surface of the right hind paw with formalin (1%). Nociception

was quantified as the number of flinches of the injected paw during 1 hour, whereas a reduction of the number of flinches was considered antinociception. Rats received a subcutaneous injection into the dorsal surface of the paw of vehicles or increasing doses of carvacrol (100-300 µg/paw). To determine whether the local antinociception induced by carvacrol was mediated by either the opioid receptors, the NO-cGMP-K^+ channels pathway or a biguanide-dependent mechanism, the effect of pretreatment (10 min before formalin injection) with the appropriate vehicles, naltrexone (opioid receptor antagonist), L-NAME (a NO synthase inhibitor; 100 µg/paw), 1 H-(1,2,4)-oxadiazolo (4,2-a) quinoxalin-1-one (ODQ)(a NO-sensitive soluble guanylyl cyclase inhibitor; 100 µg/paw), glibenclamide or glipizide (both ATP-sensitive K^+ channel blockers; K_{ir}6.1-2; 100 µg/paw), tetraethylammonium chloride (TEA) or 4-aminopyridine (4-AP) (both voltage-gated K^+ channel blockers; K_V; 100 µg/paw), apamin (a small conductance Ca^{2+}-activated K^+ channel blocker; K_{Ca}2.1-3; 2 µg/paw), and charybdotoxin (a big conductance Ca^{2+}-activated K^+ channel blocker; K_{Ca}1.1; 2 µg/paw), or metformin (a biguanide hypoglycemic; 400 µg/paw) on the antinociceptive effects induced by local carvacrol (300 µg/paw) were assessed. Carvacrol produced antinociception during both phases of the formalin test. Carvacrol antinociception was blocked by naltrexone, L-NAME, ODQ, K^+ channels blockers and metformin. In conclusion, local peripheral administration of carvacrol was able to produce significant antinociception and active the opioid receptor-NO-cGMP-K^+ channels pathway and a biguanide-dependent mechanism.

Disclosures: M.I. Ortiz: None. **G. Castañeda-Hernández:** None.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.03/Y2

Topic: D.02. Somatosensation – Pain

Support: NS080889

Title: Early life stress modulates neonatal somatosensation and the transcriptional profile of immature sensory neurons

Authors: *K. HARBOUR, M. HAYES, M. BACCEI;
Univ. of Cincinnati, Cincinnati, OH

Abstract: Approximately 9% of infants born every year in the US are admitted to the neonatal intensive care unit (NICU) where lifesaving procedures occur, but also exposure to injury and other chronic stressors. While the long-term consequences of early life stress (ELS) for adult pain sensitivity have been extensively studied, surprisingly little is known about how chronic stress acutely shapes nociceptive processing in neonates. Therefore, we investigated the short-term effects of ELS on both pain sensitivity and the transcriptomic profile of immature dorsal root ganglion (DRG) neurons. ELS was induced in C57Bl/6 mice using a neonatal limited

bedding (NLB) protocol from postnatal day (P)2 to P9, with standard bedding used as a control. Behavioral assays including Von Frey and Hargreaves were performed between P9 and P12 to measure mechanical and thermal sensitivity, respectively. Compared to age-matched control litters, NLB mice exhibited a significant increase in mechanical sensitivity, but not thermal sensitivity, with no differences between sexes detected in either behavioral assay. To identify genes whose expression are significantly altered by ELS, bilateral L3-L5 DRGs were harvested at P9 (n = 6 mice/group; balanced by sex) and bulk RNAseq analysis was conducted. Overall, 132 genes exhibited a ≥ 2-fold increase or decrease in expression after ELS with no significant sex differences observed. The differentially expressed genes were distributed across multiple functional classes including neuropeptides, voltage/ligand-gated ion channels and chemokine/chemokine receptors, including several pain- and itch-related genes such as *Il31ra*, *Trpa1*, and *Chrna6*. Most strikingly, *Sst* and *Nppb*, which are known to be highly co-localized in a subpopulation of DRG neurons implicated in chronic pain and itch, each showed a >16-fold downregulation in NLB mice compared to naïve controls. Collectively, these results yield new insight into the potential mechanisms governing the intersection between chronic stress and pain during the neonatal period.

Disclosures: K. Harbour: None. **M. Hayes:** None. **M. Baccei:** None.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.04/Y3

Topic: D.02. Somatosensation – Pain

Support: JSPS/Grant 22K06001

Title: Involvement of nociceptive TRPA1 channel in the analgesic effects of Lavender essential oil components

Authors: *M. HASHIMOTO, K. TAKAHASHI, T. OHTA;
Dept. of Vet. Pharmacology, Grad. Sch. of Vet. Medicine, Tottori Univ., Tottori, Japan

Abstract: Lavender Essential Oil (LEO) is commonly used in fragrances. It is known that LEO has anxiolytic, sedative, and analgesic actions. However, the mechanism of its analgesic action is not fully clarified. Pain signals elicited by the activation of nociceptors on peripheral neurons are transmitted to the central nervous system. In the present study, we investigated the effects of major LEO components (linalool and its acetic acid ester, linalyl acetate) on transient receptor potential ankyrin 1 (TRPA1) channel, which is important for pain signaling as nociceptors in somatosensory neurons. For detection of channel activity, the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) was measured using a fura2-based Ca^{2+} imaging system, and membrane currents were recorded by a whole-cell patch-clamp technique. Analgesic actions in individuals were examined in vivo. In mouse sensory neurons, linalool at concentrations without changing the resting

$[Ca^{2+}]_i$, reduced $[Ca^{2+}]_i$ increases induced by allyl isothiocyanate (AITC) and carvacrol, exogenous TRPA1 agonists. Linalool also suppressed Ca^{2+} responses to Prostaglandin J_2 (PGJ_2), an endogenous TRPA1 agonist to the same extent. Similar inhibitory effects of linalool were observed in cells heterologously expressed TRPA1 channel. In wild-type mice an injection of PGJ_2 to the hind paw elicited nociceptive behaviors, which were significantly diminished in TRPA1-gene deficient mice. Linalool dose-dependently reduced the PGJ_2-induced nociceptive behaviors. Similar to linalool, linalyl acetate suppressed $[Ca^{2+}]_i$ and current responses to TRPA1 agonists in cells heterologously expressed TRPA1 channel. However, the inhibitory action of linalyl acetate on AITC was greater than carvacrol. These results suggest that inhibition of nociceptive TRPA1 channel is related to the analgesic actions of linalool and linalyl acetate. Therefore, the components of LEO may be effective as lead compounds for the development of new analgesic drugs.

Disclosures: **M. Hashimoto:** None. **K. Takahashi:** None. **T. Ohta:** None.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.05/Y4

Topic: D.02. Somatosensation – Pain

Support: NIH Grant R01DA051876

Title: Decreased AC1 and increased SUR1 spinal cord expression attenuates opioid tolerance and withdrawal in mice

Authors: ***K. M. JOHNSON**, B. A. MEYER, J. MELLANG, A. L. FOWLER, A. H. KLEIN; Univ. of Minnesota, Duluth, MN

Abstract: A recent study found chronic pain has an incidence rate of 52.4 cases per 1,000 person years, which is higher than other known chronic diseases including diabetes and depression, demonstrating the high disease burden of chronic pain (Nahin et al., 2023). Although opioid analgesics are a frequently prescribed drug class, chronic opioid use can lead to abuse, dependence and overdose (Chou et al., 2015). Due to this health burden of opioids, identifying molecular targets which cause opioid tolerance and withdrawal may help chronic pain patients. Under normal physiological conditions, adenylyl cyclases are inhibited upon mu opioid receptor activation (MOR). Under long term opioid exposure and therefore continuing activation of MORs, adenylyl cyclase (AC) activity, and subsequently cAMP activity, increases. Several molecular targets downstream of cAMP, including modulation of ion channels, have been investigated for their role in opioid tolerance. Potassium channel activity, including ATP-sensitive potassium channels (K_{ATP}), are decreased under chronic opioid conditions in the nervous system. Preliminary data from our lab has shown systemic delivery of ST034307 (5mg/kg), an AC1 antagonist, improves morphine tolerance when administered chronically

(15mg/kg, twice daily), but this effect was lost in mice with conditional knock out of sulfonylurea receptor 1 (SUR1), a component of K_{ATP} channels found in the nervous system. In order to further investigate how altered AC1 function affects opioid tolerance and withdrawal via K_{ATP} channels *in vivo,* we used a viral vector strategy to downregulate AC1 (*Adcy1*) in the spinal cord using AAV9-Adcy1-shRNA concurrently with the upregulation of either SUR1 (*Abcc8*) or Kir6.2 (*Kcnj11*) using Ad-m-Abcc8 or Ad-m-Kcnj11, respectfully. Morphine dose responses (1-15 mg/kg) were significantly shifted in control vector mice (AAV9-Scramble-shRNA, Ad-m-Null) after establishment of morphine tolerance compared to dose-response curves obtained before tolerance. The increased expression of K_{ATP} channel subunits combined with the decreased AC1 expression did not significantly shift morphine dose response curves. Mice treated with AAV9-Adcy1-shRNA in conjunction with Ad-m-Abcc8 had the smallest shift in morphine dose responses, indicating both a decrease in AC1 activity paired with an increase in SUR1 can attenuate opioid tolerance and withdrawal.

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Poster

PSTR270. Nociceptors

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Program #/Poster #: PSTR270.06/Y5

Topic: D.02. Somatosensation – Pain

Support: Knut and Alice Wallenberg Foundation project no. 2019.0047
Wallenberg Center for Molecular Medicine

Title: Functional and anatomical characterization of genetically targeted myelinated nociceptors

Authors: C.-Y. CHEN[1], O. LE MOËNE[1], L. KACZMARCZYK[2], W. JACKSON[2], *M. LARSSON[1];
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Abstract: Nociceptive primary afferent fibers that are responsible for detecting different types of noxious stimuli can be broadly divided into unmyelinated C fibers and myelinated A fibers. Whereas some subclasses of C fiber nociceptor have been extensively studied, comparatively less is known about the function of myelinated nociceptors. To enable comprehensive characterization of presumed myelinated nociceptors we generated two mouse lines, Nefh:CreERT2 and NaV1.8:FlpO, that allowed for intersectional Cre- and Flp-dependent genetic targeting of a broad population of such fibers. In the skin, peripheral nerve fibers targeted via this strategy formed free nerve endings as well as circumferential nerve endings around hair follicles. In the spinal cord, a dense plexus of fibers was observed in lamina I, whereas lamina II showed a comparatively low fiber density; a moderate density of fibers was found in laminae III-IV, but lamina V notably exhibited a very low density of fibers. In lamina I, fibers often colocalized with

CGRP but in deeper laminae such colocalization was sparse. Using electron microscopy, both simple dome-shaped terminals and central terminals of synaptic glomeruli were observed to contain peroxidase targeted to these fibers. Cutaneous optogenetic stimulation of the targeted fiber population induced withdrawal reflexes and strong place aversion in a real-time place preference assay. Facial expression analysis during optogenetic stimulation revealed a pattern of facial feature changes that closely resembled those induced by optogenetic stimulation of a population of CGRP-lineage nociceptors. Unexpectedly, whereas facial features recovered to baseline rapidly after cessation of a three-minute optogenetic stimulus of the CGRP-lineage fibers, the pain-related facial expression was retained for at least three minutes after ceasing stimulation of the presumed myelinated nociceptors. These observations suggest that a broad class of myelinated nociceptors target spinal circuits that control reflexive behavior but also relay signals to supraspinal pathways associated with aversive behavior and affective aspects of pain.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.07/Y6

Topic: D.02. Somatosensation – Pain

Support: Award # B9253-C (Agency: Veterans Administration Rehabilitation Research and Development Service)
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Title: Multiple Rab GTPase subtypes are involved in Nav1.7 anterograde transport in sensory axons

Authors: *N. SARVESWARAN[1,4], D. GEBERT[2,4], S. TYAGI[2,3,4], C. BORELLI[2,4], S. LIU[2,4], F. DIB-HAJJ[2,4], S. DIB-HAJJ[2,4], S. WAXMAN[2,4];
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Abstract: Nociceptors are specialized somatosensory neurons of the peripheral nervous system that respond to injurious stimuli. Human genetic studies have demonstrated that Nav1.7, a member of the voltage-gated sodium channel family, has a crucial role in fine-tuning the excitability of these cells and subsequent perception of pain - therefore, a highly appealing target for analgesic drug development. Membrane proteins synthesized in the cell body are packaged into vesicles that move anterogradely toward distal axons for insertion along the cell surface. Rab GTPases have been implicated in cargo sorting and directing membrane traffic to specific

neuronal compartments, including several ion channels, surface receptors, and dense core vesicles containing excitatory neuropeptides. Previous work investigating 8 of the ~60 human Rab proteins showed that Nav1.7 was selectively co-transported in Rab6A-positive vesicles. However, an appreciable proportion of Nav1.7-positive vesicles did not contain Rab6A, suggesting additional Rabs could be involved in Nav1.7 anterograde transport. Here we have used the Optical Pulse-Chase Axonal Long-distance (OPAL) imaging assay to investigate Nav1.7 co-transport with three additional Rab proteins that are highly expressed in dorsal root ganglia. Our experiments show that Nav1.7 was also carried in Rab11A- and Rab15-positive vesicles but not in those containing Rab14. Moreover, we observed considerable co-trafficking of Rab6A, Rab11A, and Rab15 in the same vesicles, although they were not always transported together. Finally, we showed a significant reduction in Nav1.7 localization to Rab6A-positive vesicles when Rab6A GTPase activity was inactivated through a point mutation. Further experiments to understand the impact of this change on Nav1.7 surface insertion are ongoing. Our results reveal an association between Nav1.7 and several Rab subtypes within anterograde transport vesicles in sensory axons, and that inactivating GTPase activity of one Rab subtype can partially uncouple its relationship with Nav1.7. Importantly, the co-localization of different Rab subtypes in single transport vesicles offers a layer of redundancy so that functional Rabs can partially stand in for an inactivated isoform in regulating Nav1.7 transport.

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Poster

PSTR270. Nociceptors

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Program #/Poster #: PSTR270.08/Y7

Topic: D.02. Somatosensation – Pain

Support: NIH Grant DE23090

Title: Inflammation-induced changes in the functional properties of Aβ-fiber high threshold mechanoreceptors and Aβ-fiber low threshold mechanoreceptors in the hindpaw glabrous skin of mice

Authors: *A. YAMADA[1], A. YAMADA[1], J. LING[1], H. FURUE[2], J. G. GU[1];
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Abstract: Inflammatory conditions often lead to mechanical allodynia, a pain state that can be triggered by a gentle touch. However, the mechanism underlying mechanical allodynia is not fully elucidated. Recently, we have used Nav1.8^{ChR2} transgenic mice and show that Nav1.8^{ChR2}-positive Aβ-fiber mechanoreceptors are mostly high threshold mechanoreceptors (HTMRs) whereas Nav1.8^{ChR2}-negative Aβ-fiber mechanoreceptors are low threshold mechanoreceptors (LTMRs). In the present study, we investigated whether the functional properties of these

HTMRs and LTMRs in the hindpaw glabrous skin of Nav1.8^{ChR2} transgenic mice may be altered following inflammation induced by Complete Freund's Adjuvant (CFA). We used hindpaw glabrous skin-tibial nerve preparations and applied pressure-clamped single fiber recordings to measure mechanical sensitivity on the hindpaw glabrous skin. We found that CFA-induced inflammation impacted functional properties of both Nav1.8^{ChR2}-positive Aβ-fiber HTMRs and Nav1.8^{ChR2}-negative Aβ-fiber LTMRs in the hindpaw glabrous skin. The mechanical threshold of Nav1.8^{ChR2}-positive Aβ-fiber HTMRs was significantly lowered in the CFA group compared to the saline control group. Conversely, for Nav1.8^{ChR2}-negative Aβ-fiber LTMRs, their mechanical threshold significantly increased in the CFA group. Our findings raise the possibility that changes in the mechanical threshold of both Aβ-fiber HTMRs and Aβ-fiber LTMRs may contribute to mechanical allodynia following tissue inflammation, providing a new insight into inflammatory pain. The study is supported by NIH R01 DE023090 to JGG.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.09/Y8

Topic: D.02. Somatosensation – Pain

Support: ZIACL090033
ZIACL090035

Title: Syntaxin1a overexpression as the basis for pain insensitivity in individuals with 7q11.23 duplication syndrome

Authors: *M. J. IADAROLA[1], M. R. SAPIO[2], A. J. LOYDPIERSON[2], J. FEHRENBACHER[3], M. R. VASKO[3], D. MARIC[4], D. P. EISENBERG[5], T. A. NASH[6], J. S. KIPPENHAN[6], C. B. MERVIS[7], A. J. MANNES[2], M. D. GREGORY[8], K. F. BERMAN[8];
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Abstract: While genetic mutations leading to pain insensitivity phenotypes are rare, the underlying molecular biology is often used to validate analgesic drug candidates. Pain insensitivity generally results from Mendelian loss-of-function mutations in genes expressed in nociceptive (pain-sensing) dorsal root ganglion (DRG) neurons that connect skin and deep tissues to the spinal cord. Using this peripheral DRG frame of reference, we report on pain

insensitivity in individuals with 7q11.23 duplication syndrome (Dup7) who have three copies of the ~1.5 megabase Williams syndrome (WS) critical region at chromosomal locus 7q11.23, which contains ~26 genes. Our study shows that, based on parental reports, some people with Dup7 are pain insensitive following serious injury to skin, bones, teeth, or viscera. In contrast, their diploid siblings (with two copies of the 7q11.23 WS critical region) and people with WS (having one copy of the same genes) show standard reactions to painful events. Here we use a converging series of human assessments, and cellular, biological, and transcriptomic methodologies that implicate the *STX1A* gene, which codes for the synaptic vesicle fusion protein Syntaxin1A, as the candidate gene in the 7q11.23 copy number variant (CNV) that underlies this phenotype, and the DRG as site mediating the nociceptive dysfunction. First, co-expression profiling showed enrichment of murine *Stx1A* expression in the TRPV1+ population of nociceptive afferents which are critical for cutaneous thermal nociception and deep tissue damage pain. Next, overexpression of *STX1A* by lentiviral transduction of rat primary afferent neurons yielded a reduction in capsaicin-evoked CGRP release, supporting a functional association between STX1A and neuropeptide release from TRPV1+ DRG neurons. Further, anatomical colocalization of *STX1A* with *TRPV1+* neuronal populations was demonstrated by multiplex fluorescent in situ hybridization of human DRG. Finally, in human cell lines from +/-, +/+, and +/+/+ individuals (i.e., WS, diploid, and Dup7, respectively) we observed a clear gene dosage effect with increasing copy number (p-adj=$1.5x10^{-10}$). The progressive increase was specific for STX1A, and expression of none of the 18 other syntaxin analogs was altered (all p-adj's>0.1). The present data suggest *STX1A* overexpression compromises synaptic vesicle fusion and transmitter exocytosis in nociceptive afferent neurons, thereby producing a "genetic analgesia" in affected individuals. As such, this implicates several biochemical pathways as potential targets for pain control.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.10/Y9

Topic: D.02. Somatosensation – Pain

Support: NS120395

Title: Understanding the role of prolactin in stress-induced neuronal sensitization and pain outcomes in a preclinical model of post-surgical pain

Authors: *M. DOLATYARI[1], H. J. STRATTON[1], C. KOPRUSZINSKI[1], A. MOUTAL[2], E. NAVRATILOVA[1], F. PORRECA[1,3];

[1]Pharmacol., Univ. of Arizona, Tucson, AZ; [2]St. Louis Univ., St. Louis Univ., St Louis, MO; [3]Neurol., Mayo Clin., Phoenix, AZ

Abstract: Women experience pain more frequently than men, but the biological mechanisms behind these sex differences in pain are not yet fully understood. Post-operative pain (POP) presents a major unmet clinical problem and women frequently report more POP than men – possibly a result of increased or sustained nociceptor sensitization after surgery. Prolactin (PRL), a neurohormone, circulates at higher levels in women and has an established role in driving neuronal sensitization. The existing literature suggests that experiencing stress before a surgical procedure may be associated with poorer POP outcomes. Since stress has been shown to trigger the release of PRL, we hypothesized that presurgical blockade of PRL signaling could improve pain outcomes after surgery. We sought to determine whether stress could prolong the recovery from post-surgical pain in male and female C57Bl6 mice. We utilized restraint stress (RS) to produce sensitization and the plantar incision model (PLI) as a model of postoperative pain. Mechanical hypersensitivity was evaluated using von Frey (VF). In all studies, experimenters were blind to the treatment conditions, animals were randomly assigned to treatment groups, and unblinding was performed after all data were analyzed. We found that stress significantly prolonged the recovery of withdrawal frequency to baseline levels in animals that were stressed compared to unstressed control mice. To investigate the corresponding electrophysiological changes associated with this behavioral hypersensitivity, dorsal root ganglia innervating the paw were dissected and cultured then incubated overnight with a subthreshold dose of PRL. We found that mice exposed to RS had significantly increased excitability compared to non-stressed mice. To determine whether PRL was responsible for prolonging the recovery from post-surgical pain, we used cabergoline to inhibit the release of circulating PRL. Mice received i.p. cabergoline treatments at 1.2 mg/kg 2 hours before RS, PLI, and after von Frey tests on days 4, 6, 8, and 10 after RS and days 2 and 4 after PLI. Controls received the respective vehicles at 10 mL/kg. Treatment with cabergoline blocked stress-induced increase in response frequency and post-surgical hypersensitivity in female mice, but not male mice. DRG neurons were harvested from these animals, and we found that those treated with vehicle had increased excitability in response to low-dose PRL. Still, this effect was blocked in female mice treated with cabergoline. In conclusion, we have found that PRL is involved in stress-induced POP prolongation, suggesting that PRL could be targeted to alleviate pain selectively in female patients.

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Poster

PSTR270. Nociceptors

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Topic: D.02. Somatosensation – Pain

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Susan Samueli Integrative Health Institute's Scholar Award

Title: Lysophosphatidic acid contributes to hyperalgesia in a humanized mouse model of sickle cell disease through direct sensitization of dorsal root ganglia neurons

Authors: *V. VIATCHENKO-KARPINSKI[1], M. JOHNS[1], I. A. KHASABOVA[1], S. G. KHASABOV[1], K. GUPTA[2], D. A. SIMONE[1];
[1]Sch. of dentistry, Univ. of Minnesota, Twin Cities, Minneapolis, MN; [2]Dept. of Med., Univ. of California, Irvine, CA

Abstract: Sickle cell disease (SCD), the most common hemoglobinopathy, is characterized by hemolysis, vaso-occlusion, vasculopathy, ischemia-reperfusion injury, inflammation, and pain. Pain is the dominant clinical symptom of SCD and the most common cause of hospitalization. Transgenic mouse models of SCD recapitulate many disease features, including chronic pain. Homozygous HbSS-BERK mice were used to study the contribution of lysophosphatidic acid (LPA), an endogenous lipid pain mediator, to chronic hyperalgesia in SCD. HbSS mice express >99% human sickle hemoglobin and mirror symptoms of human SCD. HbAA mice expressing normal human hemoglobin were used as a control. Hyperalgesia in HbSS mice was accompanied by increased plasma level of LPA, and administration of LPA produced hyperalgesia in control HbAA mice. Mechanical hyperalgesia was defined by a decrease in paw withdrawal threshold, and heat hyperalgesia was characterized by a reduction in paw withdrawal latency to radiant heat. Considering that LPA exerts its effects by binding to LPA_{1-6} receptors (LPAR), among which DRG neurons widely express $LPAR_1$, qPCR was used to determine the expression of $LPAR_1$ in DRG. Hyperalgesia in HbSS mice was associated with increased expression of $LPAR_1$ mRNA in DRGs. Systemic administration of AM966, an $LPAR_1$ antagonist, attenuated chronic hyperalgesia in HbSS mice. The direct effect of LPA on dissociated DRG neurons was investigated using the patch-clamp recording. Nociceptive neurons were detected by action potential (AP) shape, membrane capacitance, and size (area$\leq$500 μm^2). In contrast to HbAA mice, DRG neurons from HbSS mice exhibited spontaneous APs and increased excitability more than HbAA mice, defined by lower rheobase and depolarized resting membrane potential (RMP). Similar results were observed when DRG neurons from HbAA mice were treated with LPA (10 μM) for 24 hours in vitro. These data suggest that LPA contributes to hyperalgesia in SCD by sensitizing DRG neurons.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.12/Y12

Topic: D.02. Somatosensation – Pain

Title: Patch clamp profiling the functional properties of human iPSC-derived nociceptors

Authors: *A. E. SNYDER[1], P. J. GANDHI[1], D. LIU[1], C. TIAN[1], C. M. PETROSKI[1], V. TRUONG[2], P. WALSH[2], R. E. PETROSKI[1];
[1]Neuroservices-Alliance, San Diego, CA; [2]Anatomic Inc., Anatomic Inc., Minneapolis, MN

Abstract: According to the National Institute of Neurological Disorders and Stroke, 100 million adults in the United States suffer from chronic pain. One way to study pain is to use human iPSC-derived nociceptors as an in vitro model, but it is important to characterize the cell properties to understand their utility. Here, we profiled the functional properties of human iPSC-derived nociceptors using whole cell patch clamp recordings at different timepoints (1-8 weeks) to determine the time course for the development of a mature neuronal phenotype. Nociceptors were thawed and plated at a low density, with a subset plated on a monolayer of rat astrocytes. Upon establishing the whole cell configuration, we measured the passive membrane properties for every cell including membrane capacitance (Cm), membrane resistance (Rm) and resting membrane potential (RMP). We also recorded spontaneous action potential firing as well as intrinsic excitability using a rheobase protocol. Additionally, we evaluated the expression of voltage-gated sodium and potassium currents. We recorded from over 100 sensory neurons from 1-8 weeks in vitro. Human nociceptors plated at low density on rat astrocytes appeared healthier and were easier to patch compared to neurons plated without astrocytes. Nociceptors grew larger with time in culture as evidenced by an increase in Cm, with decreased Rm. The RMP became more hyperpolarized after three weeks and remained stable thereafter. Little spontaneous activity was observed in cells at every developmental timepoint, as would be expected from sensory neurons. The nociceptors were excitable, however, as action potentials were elicited with depolarizing current injections. Further, the amount of current injection required to elicit the first action potential (rheobase) increased over developmental time, as expected from neurons with lower Rm. Additionally, nociceptors at all developmental timepoints exhibited sodium currents. The voltage-dependent sodium current amplitudes increased with time in culture, while the peak sodium current density (pA/pF) remained stable. We also evaluated the presence of TTX-R sodium currents at 5-8 weeks in vitro and detected their presence at all evaluated time points. The proportion of TTX-R among nociceptors varied. Overall, we determined that these human iPSC-derived nociceptors display a mature developmental phenotype by three weeks in culture, with appropriate RMPs, the ability to evoke activity, and the demonstration of TTX-R and TTX-sensitive Na currents.

Disclosures: **A.E. Snyder:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **P.J. Gandhi:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **D. Liu:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **C. Tian:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **C.M. Petroski:** A. Employment/Salary (full or part-time):; Neuroservices-Alliance. **V. Truong:** A.

Employment/Salary (full or part-time):; Anatomic Incorporated. **P. Walsh:** A.
Employment/Salary (full or part-time):; Anatomic Incorporated. **R.E. Petroski:** A.
Employment/Salary (full or part-time):; Neuroservices-Alliance.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.13/Y13

Topic: D.02. Somatosensation – Pain

Support: VEGA 1/0065/23

Title: Functional Characterization of C-fiber Subtypes in Mouse Skin

Authors: *D. JURCAKOVA[1,2], M. GRENDAR[1,3], B. J. UNDEM[4];
[1]Comenius Univ., Martin, Slovakia; [2]Jessenius Fac. of Med., Dept. of Pathological Physiol., Martin, Slovakia; [3]Biomed. Ctr. Martin, Jessenius Fac. of Med., Martin, Slovakia; [4]Asthma And Allergy Ctr., Johns Hopkins Univ., Baltimore, MD

Abstract: Nociceptive neurons serve as specialized detectors of a plethora of potentially harmful internal and external stimuli and comprise a highly diverse cell population. In the recent years, transcriptional profiling of dorsal root ganglia neurons identified 4 -10 molecularly distinct nociceptive-like subtypes. While these studies inform nerve phenotypes, they are at best cautiously translated to nerve function. Moreover, these studies have focused on the whole ganglia comprising neurons innervating various peripheral tissues. In this study, we focused on functional characterization of C-fiber subtypes based on the responsiveness of nerve terminals innervating the dorsal skin of the mouse. We used *ex vivo* mouse skin-spinal nerve preparation to evaluate responses of 232 individual C-fibers to 15 chemical (chloroquine (CQ), BAM8-22, histamine, bradykinin, ß-alanine, serotonin, ATP, lysophosphatidic acid and TRPV1, V3, V4, A1, C3/6, M2, M8 channel) agonists as well as mechanical stimulation. Based on the mechanical sensitivity, cutaneous C-fibers can be subcategorized into low mechanical threshold (C-LTMs; 8%) and high mechanical threshold (C-HTMs; 92%) C-fibers. C-LTMs were unresponsive to all chemical mediators except the TRPV4 agonist GSK1016790A that discharge C-LTMs with a 3-fold greater potency than other C-fibers (95±24 APs (n=8) vs 32±4 APs (n=36), respectively).The C-HTMs could be, based on the chemical stimulus profile, subdivided broadly into two subgroups, one responding strongly to pruritogens such as chloroquine, histamine or BAM8-22 (n=72, 31%), but not other mediators; the other failing to respond to pruritic stimuli, but respond strongly to ATP or serotonin. Of the latter, about 50% also respond to the MrgprD stimulant ß-alanine; these ß-alanine responsive C-fibres were the only subtype that responded to the TRPV3 channel agonist farnesyl pyrophosphate (10µM). We hypothesize that activating the chloroquine/histamine sensitive C-HTMs likely evokes, relatively selectively, pruritic sensations; the more promiscuous, CQ/histamine insensitive C-fibres likely subserve more varied sensations including cutaneous pain.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

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Program #/Poster #: PSTR270.14/Y14

Topic: D.02. Somatosensation – Pain

Support: R01NS119476

Title: Targeted gene delivery to nociceptors

Authors: J. LI[1], **J. X. J. LUO**[1], *P. BHATIA[1], J. WANG[1], E. SEMIZOGLOU[1], L. YANG[1], M. XU[1], L. MCELRATH[2], S. HRVATIN[2], W. RENTHAL[1];
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Abstract: Targeted gene delivery to nociceptors
Jia Li, X. Jay Luo, Parth Bhatia, Jiaxiang Wang, Eva Semizoglou, Lite Yang, Mengyi Xu, Lorna McElrath, Sinisa Hrvatin, William Renthal
Chronic pain affects over 25 million adults in the United States and is a major cause of disability. Currently available pain treatments such as opioids are often ineffective and associated with unacceptable side effects including respiratory depression and addiction. Viral-based gene therapy offers several attractive advantages in treating refractory pain, as viruses can be engineered to deliver a wide range of molecular cargo capable of regulating neuronal excitability. To develop novel nociceptor-specific viral tools, we performed single-nucleus RNA sequencing and assay for transposase accessible chromatin (ATAC) sequencing on the mouse dorsal root ganglion (DRG) to identify nociceptor-specific molecular features. Specifically, 7,376 epigenomically profiled nuclei from male and female mice were sequenced and analyzed. We identified >10,000 nociceptor-specific regions of chromatin accessibility. Gene regulatory network analyses of these data identified transcription factors that are significantly enriched in DRG nociceptor subtypes, including *EBF1, POU4F3, JUN, MEF2C, NFIA,* and *ISL2*. After prioritization and screening of putative nociceptor-specific enhancers, each was cloned into adeno-associated (AAVs) and delivered to DRGs in mice. *In situ* hybridization of viral GFP and nociceptor markers were used to determine which enhancers drive reporter expression preferentially in nociceptor subtypes. We identified three enhancers that drive expression in DRG nociceptors with significantly more selectivity than control promoters. Ongoing studies are using our lead enhancers to drive the expression of chemogenetic actuators to silence the activity of nociceptors in vitro and in vivo. These nociceptor-selective gene therapy vectors are likely offer significant safety advantages over currently available viral vectors for the treatment of refractory chronic pain.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.15/Y15

Topic: D.02. Somatosensation – Pain

Support: NIH Grant U19NS130608

Title: The MNK-eIF4E Signaling Axis Mediates IL6-Driven Enhancements in Neuronal Protein Synthesis within Human Dorsal Root Ganglion Explants

Authors: *G. TORRIJOS[1], L. F. COOK[1], M. E. MITCHELL[1], L. HE[2], J. M. MWIRIGI[3], S. SHIERS[4], T. PRICE[5];
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Abstract: Every day, billions of people throughout the world must endure their debilitating chronic pain symptoms due to the deficit in adequate therapeutic options. Pain symptoms including hypersensitivity and spontaneous pain often severely reduce the daily quality of life for these patients and the ability of these individuals to thrive. A major limitation is the poor success of therapeutics developed in pre-clinical rodent models in clinical settings. Therefore, generating effective treatments requires the study of potential target pathways in living human tissues. Pain symptoms are thought to arise from maladaptive plasticity in pain pathways that drives sustained hyperexcitability in the nociceptor in the dorsal root ganglion (DRG), primary sensory neurons in the PNS that detect and transmit pain-associated activity to the CNS. Cytokine Interleukin 6 (IL-6) is a critical driver of long-term maladaptive nociceptor plasticity in a variety of pain pathologies. In nociceptors, a key long-term plasticity mechanism is the control of gene expression through activity-dependent translation. In rodent models, IL-6 signaling induces protein synthesis in nociceptors by engaging MNK phosphorylation of eIF4E. Engagement of the MNK-eIF4E signaling axis induces polyribosome formation shifting the nociceptor translatome to support long-term hyperexcitability in chronic pain states. Blocking MNK phosphorylation of eIF4E either genetically or pharmacologically with peripheral administration of inhibitors like eFT508 ameliorates hypersensitivity. However, the role of this pathway in human nociceptors is only beginning to be revealed. Here, we tested whether a 20 min pulse with IL-6 (10 ng/mL) increases neuronal protein synthesis via the MNK-eIF4E signaling axis in living human DRG explants. We used Fluorescent Noncanonical Amino Acid Tagging (FUNCAT) to detect nascent proteins and immunofluorescence to detect changes in phosphorylated eIF4E (p-eIF4E). We demonstrate that IL6 induces protein synthesis and enhances p-eIF4E in a subset of neuronal

somata in human DRG explants. Furthermore, we show that a significant proportion of neurons exhibit simultaneous increases in both p-eIF4E and nascent proteins only in IL-6-treated explants. We also found that the addition of the MNK1/2 inhibitor eFT508 (100 nM) blocks this effect, indicating that MNK1/2 is a critical driver of these IL-6-induced increases. Overall, these data suggest that targeting this pathway in the PNS has the potential to inhibit or mitigate IL-6 engagement of maladaptive nociceptor plasticity mechanisms that drive their persistent excitability in chronic pain patients.

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Poster

PSTR270. Nociceptors

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.16/Y16

Topic: D.02. Somatosensation – Pain

Support: NIH IRP Grant CL090034
NIH IRP Grant CL090035
NIH IRP Grant CL090033

Title: The skin-nerve transcriptomic interface: insights from human intra-operative tissue sampling during long thoracic surgeries

Authors: *M. R. SAPIO[1], A. F. DOMENICHIELLO[2], A. P. MANALO[1], T. GOTO[3], D. MARIC[4], T. S. WILLIAMS[1], D. S. SCHRUMP[5], J. L. DAVIS[6], J. M. HERNANDEZ[6], A. M. BLAKELY[6], A. J. MANNES[1], M. J. IADAROLA[1];
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Abstract: The question of how tissue responds to injury is fundamental to understanding the initial molecular events in pain, wound healing, and inflammatory processes that contribute to post-operative pain and recovery. Previous work from our lab in a rat incision model used transcriptomics and multiplex labeling to uncover several pathways initiated by surgical incision that signal to DRG neurons and to local tissues, recruiting immune cells, and driving early hyperalgesic pathways. These proof-of-concept rodent studies led to several candidate molecules that may be of interest for pain and wound-healing drug development efforts. However, the degree of overlap between rat and human tissue incision models has not been carefully assessed from a molecular point of view. In this study, we collected tissue from N=12 (5M, 7F) patients undergoing surgeries with a planned duration longer than 4 hours. We sampled tissue from the wound edge serially at staged intervals to capture the time course of induction and assess patterns of gene regulation over time. The longest case finished at 12 hours 44 minutes. We

selected out highly expressed, strongly induced transcripts encoding secreted proteins, and further refined for proteins likely to signal to DRG neurons based on transcriptomic evidence. This strategy highlights gene induction from the damaged tissue whose products can directly signal to the nociceptive afferents, which could be involved in nociceptive transmission, sensitization of the nerve endings, and driving the neuroinflammatory processes arising from tissue injury. Overall, we identified a high degree of correspondence between most of these induction events between rat and human, although the overall pattern of induction in human skin was markedly different from currently used incision protocols in rodents. The major reason for this may be the brief duration of tissue incision used in the rodent incision model, which does not continually traumatize the wound edge, but rather generally assesses longer-term consequences of tissue injury. We found that the most significant genes induced by this paradigm were cytokine signaling pathways including those for interleukins and the pleiotropic cytokine oncostatin M. Additionally, several genes were strongly induced related to innate immune activation, the initiation of wound healing, and neutrophil recruitment. We are investigating the role of these pathways by back-translating the most critical findings into longer-term rodent wound models. This abstract is based on a clinical trial registered at ClinicalTrials.gov (NCT04224870).

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Poster

PSTR270. Nociceptors

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.17/Y17

Topic: D.02. Somatosensation – Pain

Support: Grunenthal

Title: Identification of neuronal populations in dorsal root ganglia using spatial transcriptomics: Comparison between pig and human species

Authors: *M. MANCILLA MORENO, D. TAVARES FERREIRA, N. INTURI, S. SHIERS, I. SANKARANARAYANAN, A. ARENDT-TRANHOLM, J. MWIRIGI, T. J. PRICE;
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Abstract: Animal models are used to probe basic pain mechanisms in the dorsal root ganglia (DRG) and to test the efficacy of drugs at the preclinical stage. Although rodent models provide invaluable insight for pain research, they often fail to mirror relevant human conditions, leading to poor translatability of promising therapeutic targets. To address this, pigs are considered an alternative model due to their comparability to humans. Pigs and humans share similar neural

pathways for Aδ- and C-fibers, distribution of free sensory nerve endings, axonal excitability properties, and conduction velocities of nociceptors. Nevertheless, specific neuronal subpopulations in pig DRGs have not been identified. Research studies characterizing the molecular profile of DRGs in rodents yield great insight on the heterogenous neuronal populations. Spatial transcriptomic tools offer an advantage over other next generation sequencing technologies because they capture the physical landscape of cell populations, allowing us to localize RNA transcripts within tissue and enhance our understanding of cell-to-cell interactions. This study seeks to comprehensively characterize neuronal subpopulations in pig DRGs and compare their evolutionary divergence from human DRGs to better assess the translatability of our preclinical pain models. We sectioned and stained 16 fresh frozen pig DRGs (Sus scrofa) with eosin and hematoxylin (H&E) to assess the quality of the tissue and the morphology of the neurons. We used the Visium Spatial Gene Expression kit to generate a near single-neuron spatial resolution. After sequencing, we selected barcodes overlapping neurons using the 10x Loupe Browser platform. Low quality cells with low counts were filtered out during quality control. Finally, we performed computational analysis using Seurat to integrate the datasets and perform neuronal clustering. We used visium spatial transcriptomics and identified 12 distinct clusters corresponding to neuronal populations including nociceptors, proprioceptors, among others. We compared them to those in humans and identified cross-species similarities and differences. We utilized our lab's published spatial transcriptomic dataset on human DRGs from healthy organ donors. Using computational approaches, we characterized neuronal subpopulations in pig DRGs using established markers from the reference human DRG dataset. Different neuronal populations were identified and compared across species. In addition to highlighting evolutionary differences, we also anticipate that this work will allow us to refine pig models, thus increasing translational efficiency of molecular pain research.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.18/Y18

Topic: D.02. Somatosensation – Pain

Title: Exploring interactions between enteric glia, mast cells, and DRG neurons in a colitis pain model

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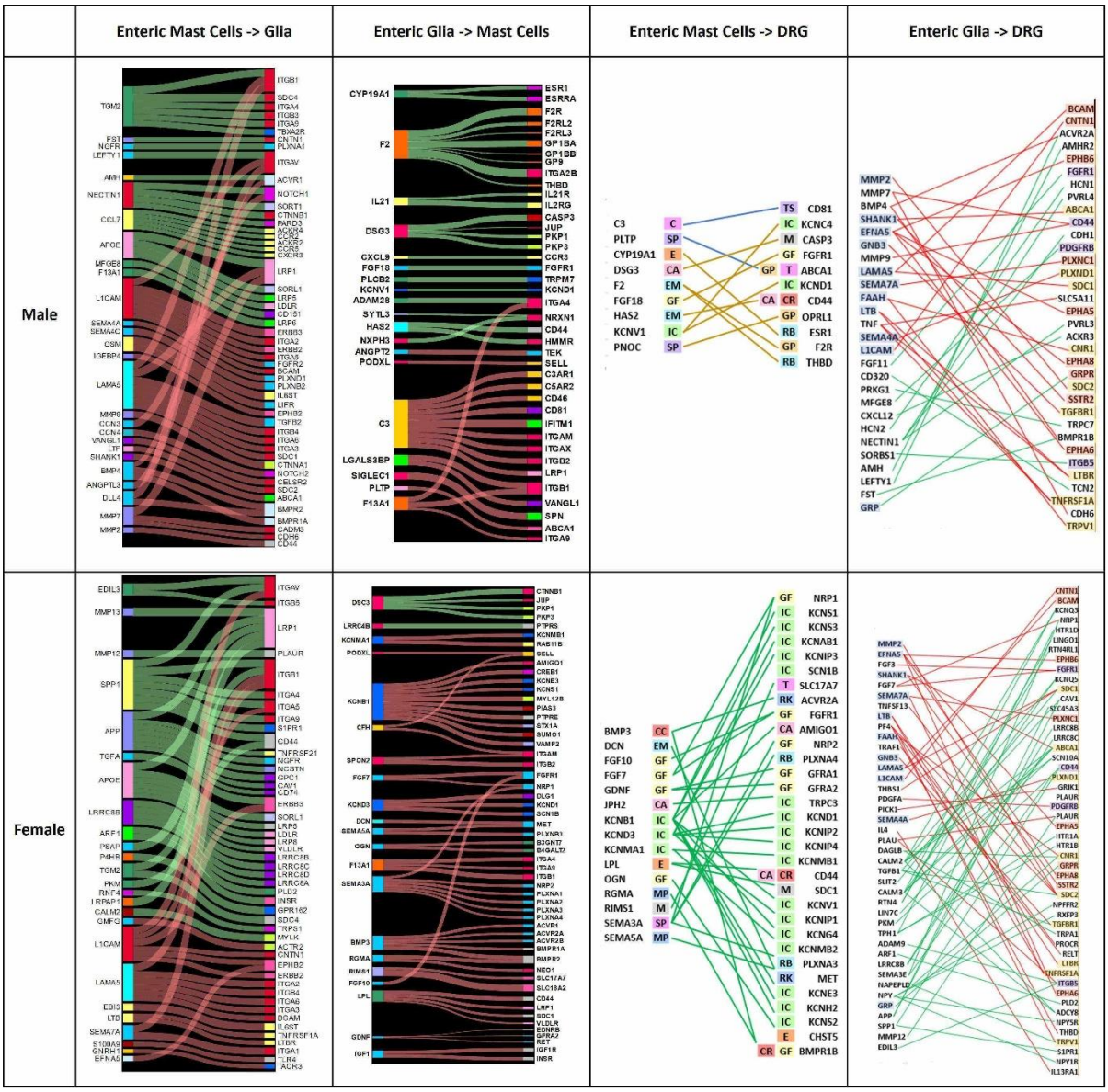
Abstract: Chronic abdominal pain due to gut inflammation affects several million Americans, especially those with IBS or IBD. However, there is a lack of therapeutics that both effectively treat this pain and avoid severe adverse effects. Here, we aim to study interactions in the colon that promote pain signaling by DRG sensory neurons and have generated a 3-way interactome of potential ligand-receptor interactions between enteric mast cells, enteric glia, and colon-innervating DRG neurons to elucidate how the enteric cells may be signaling to neurons and how they may be activating each other to sensitize nociceptors. Ligands and receptors on glia and mast cells were identified from TRAP-Seq datasets from mice that were handled normally and mice that had developed colonic inflammation after enduring stress due to neonatal maternal separation. This work lays the groundwork for future studies that will validate some of these interactions and identify therapeutic targets for chronic abdominal pain states..



Disclosures: K. Mazhar: None. **B.D. Gulbransen:** None. **A.J. Moeser:** None. **T.J. Price:** None.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.19/Y19

Topic: D.02. Somatosensation – Pain

Support: U19NS130608

Title: IL-6-Driven MNK-eIF4E signaling drives activity-dependent protein synthesis in human DRG neurons from diabetic organ donors

Authors: *M. E. MITCHELL[1], L. F. COOK[2], G. TORRIJOS[3], L. HE[4], J. M. MWIRIGI[5], S. SHIERS[6], T. PRICE[7];
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Abstract: Diabetic neuropathic pain is the most common form of neuropathic pain, but no mechanism-based therapeutics have been approved to treat this form of pain. Spontaneous pain is the most destructive aspect of pain in these patients, having a great impact on quality of daily life. A critical origin of this pathology is persistent hyperexcitability of primary nociceptors in the dorsal root ganglion (DRG). This shift in function may arise from damage signal-driven remodeling of translation regulation causing nociceptor spontaneous activity. Cytokine interleukin-6 (IL-6) signaling plays a central role in diverse chronic pain disorders and IL-6 family cytokines are upregulated in the DRG of people with diabetic neuropathic pain. In humans and rodents, IL-6 signaling engages MNK phosphorylation of eIF4E (p-eIF4E) to initiate activity-dependent protein synthesis which increases nociceptor excitability. The resulting hypersensitivity is ameliorated by genetic block of this axis in mice or by MNK1/2 inhibitors like eFT508 in rodents and human neurons. Our work in living human DRG explants demonstrated that in a subset of DRG neurons (68%), IL-6 treatment (20min; 10ng/mL) enhances somatic p-eIF4E and nascent proteins using Fluorescent Non-Canonical Amino Acid Tagging (FUNCAT). MNK-eIF4E signaling is a critical driver of this since MNK1/2 inhibitor eFT508 (100 nM) blocked this effect. Because IL-6 signaling is a central contributor to disease progression in diabetic neuropathy, we asked whether this response is exaggerated in DRG explants from diabetic organ donors. We found that in DRG neurons exhibiting enhanced p-eIF4E, the subset with concomitantly increased nascent proteins was increased in explants from diabetic (~99%) vs non-diabetic (~80%) donors. We also found a smaller number of neurons exhibited increased p-eIF4E without nascent protein increases (diabetic 1.2%; non-diabetic 19%). ROC-AUC analysis showed p-eIF4E is an effective predictor of enhanced nascent proteins in diabetic (~0.99) compared to healthy (~0.61) tissues. This suggests that DRG neurons in diabetic donors exhibit translation regulation remodeling shifting toward MNK-eIF4E-driven

translation. Overall, the work supports the conclusion that MNK inhibitors could be tested for the treatment of diabetic neuropathic pain in clinical trials.

Disclosures: **M.E. Mitchell:** None. **L.F. Cook:** None. **G. Torrijos:** None. **L. He:** None. **J.M. Mwirigi:** None. **S. Shiers:** None. **T. Price:** None.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.20/Y20

Topic: D.02. Somatosensation – Pain

Support: NIH Grant U19NS130608

Title: Predictions on human lumbar intervertebral disc to DRG signaling underlying pain production in discogenic low back pain

Authors: ***J. LESNAK**, K. MAZHAR, T. J. PRICE;
Univ. of Texas at Dallas, Richardson, TX

Abstract: Chronic low back pain (LBP) is the leading cause of disability worldwide, however current treatments are inadequate. Intervertebral disc degeneration is the proposed pathophysiology in 40% of LBP cases and is classified as discogenic LBP. Single cell RNA sequencing of intervertebral discs identified 12 unique cell clusters including 7 subsets of nucleus pulposus, 2 subsets of annulus fibrosus, and a subset of fibrochondrocyte cells. Individuals with discogenic LBP have a higher prevalence of a subset of nucleus pulposus cells marked by increased catabolic and pro-inflammatory activity. However, how each of these cell types contributes to discogenic LBP is unknown. Therefore, we used our ligand-receptor interactome to generate hypotheses on how each cell type from degenerating intervertebral discs could be signaling to DRG neurons to drive pain production. Differentially expressed genes between individuals with and without discogenic LBP were determined within each intervertebral disc cell cluster from Gene Expression Omnibus data set GSE222182. Genes that were upregulated in individuals with LBP were inputted into the ligand-receptor interactome which intersects ligand genes with corresponding receptors on DRG neurons. Interactions were filtered to include ligand-receptor interactions that only occurred on nociceptors in DRGs. PANTHER classification was used to categorize the gene function for both the ligand and receptor in the interaction pair. The analysis revealed several ligand-receptor interactions between nucleus pulposus, annulus fibrosus, and fibrochondrocytes with DRGs. Nucleus pulposus cells had upregulation of genes encoding osteopontin (*SPP1*) and inhibin A (*INHBA*), both of which are implicated in pain generation and bind to multiple receptors on DRGs. These nucleus pulposus cell clusters also had upregulation of several genes which were categorized as cytokine, chemokine, and growth factors thus demonstrating a pro-inflammatory profile. Interactions between annulus fibrosus cells and DRGs revealed ligand-receptor pairs whose

function were classified as extracellular matrix producing including collagen (*COL6A, COL9A*) and biglycan (*BGN*). The interactome revealed fibrochondrocytes had upregulation of genes encoding heat shock proteins (*HSP90, HSPA1A*) and alarmins (*S100A10*) which bind to receptors on DRGs. The interactome analysis revealed several ligand-receptor pairs between intervertebral discs and DRGs which could be driving the production of discogenic LBP. Future work will explore these pathways through molecular experiments involving human intervertebral discs and DRGs.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.21/Z1

Topic: D.02. Somatosensation – Pain

Title: Development of a human sensory neuron multi-electrode array (MEA) assay for phenotypic drug screening

Authors: L. BUTLER[1], D. MAGNANI[1], V. TRUONG[2], P. WALSH[2], J. ANTON[1], C. MANSAT-BHATTACHARYYA[1], ***R. BURLEY**[1], O. FEDORENKO[1], M. IOVINO[1]; [1]Charles River Labs., Little Chesterford, United Kingdom; [2]Anatomic Inc., Anatomic Inc., Minneapolis, MN

Abstract: Multi-electrode arrays (MEA) can be utilised in drug discovery to provide a link from *in vitro* screening to *in vivo* testing, safety assays, or by modelling the functional impacts of disease associated variants. Peripheral sensory neurons are of particular interest in both pain and peripheral neuropathies. Here we functionally characterise human iPSC derived peripheral sensory neuronal cultures using the Maestro Pro (Axion BioSystems). Neuronal activity was measured routinely over prolonged culture where neurons showed a low spontaneous firing rate and burst frequency, consistent with literature data. Time course bulk RNA sequencing data indicates the presence of relevant sensory neuron ion channels, TPRV1, Nav1.7 and Nav1.8, after one week of maturation and comparison with primary DRG shows molecular similarities. We confirmed pharmacological response indicating functional activity of these ion channels at week 3 onwards using MEA. These data show promising results for functional assessment *in vitro* of peripheral neuronal cultures and pathological pain and look suitable for the application of drug discovery and validation.

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Poster

PSTR270. Nociceptors

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Program #/Poster #: PSTR270.22/Z2

Topic: D.02. Somatosensation – Pain

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National Institute of Neurological Disorders and Stroke U19NS130617
National Institute of Neurological Disorders and Stroke U19NS130608
National Institute of Neurological Disorders and Stroke U19NS130607

Title: Harmonized cross-species cell atlases of trigeminal and dorsal root ganglia

Authors: *S. BHUIYAN[1], M. XU[1,2], L. YANG[3], E. SEMIZOGLOU[1], P. BHATIA[1], K. PANTALEO[1], I. TOCHITSKY[4], A. JAIN[5], B. ERDOGAN[6], S. BLAIR[6], V. CAT[6], J. M. MWIRIGI[7], I. SANKARANARAYANAN[7], D. TAVARES FERREIRA[7], U. GREEN[8], L. MCILVRIED[9], B. A. COPITS[3], Z. J. BERTELS[3], J. DEL ROSARIO[3], A. J. WIDMAN[3], R. SLIVICKI[3], J. YI[3], C. J. WOOLF[5], J. LENNERZ[8], J. WHITED[6], T. J. PRICE[7], R. W. GEREAU, IV[3], W. RENTHAL[1];
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Abstract: Peripheral sensory neurons in the dorsal root ganglion (DRG) and trigeminal ganglion (TG) are specialized to detect and transduce diverse environmental stimuli including touch, temperature, and pain to the central nervous system. Recent advances in single-cell RNA-sequencing (scRNA-seq) have provided new insights into the diversity of sensory ganglia cell types in rodents, non-human primates, and humans, but it remains difficult to compare transcriptionally defined cell types across studies and species. Here, we built cross-species harmonized atlases of DRG and TG cell types that describe 18 neuronal and 11 non-neuronal cell types across 6 species and 19 studies. We then demonstrate the utility of this harmonized reference atlas by using it to annotate newly profiled DRG nuclei/cells from both human and the highly regenerative axolotl. We observe that the transcriptomic profiles of sensory neuron subtypes are broadly similar across vertebrates, but the expression of functionally important

neuropeptides and channels can vary notably. The new resources and data presented here can guide future studies in comparative transcriptomics, simplify cell type nomenclature differences across studies, and help prioritize targets for future pain therapy development.

Disclosures: **S. Bhuiyan:** None. **M. Xu:** None. **L. Yang:** None. **E. Semizoglou:** None. **P. Bhatia:** None. **K. Pantaleo:** None. **I. Tochitsky:** None. **A. Jain:** None. **B. Erdogan:** None. **S. Blair:** None. **V. Cat:** None. **J.M. Mwirigi:** None. **I. Sankaranarayanan:** None. **D. Tavares Ferreira:** None. **U. Green:** None. **L. McIlvried:** None. **B.A. Copits:** None. **Z.J. Bertels:** None. **J. Del Rosario:** None. **A.J. Widman:** None. **R. Slivicki:** None. **J. Yi:** None. **C.J. Woolf:** F. Consulting Fees (e.g., advisory boards); Lundbeck, QurAlis, Axonis, Tafalgie Therapeutics. **J. Lennerz:** None. **J. Whited:** None. **T.J. Price:** 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.; Abbvie and Merck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Doloromics. **R.W. Gereau:** F. Consulting Fees (e.g., advisory boards); Doloromics. **W. Renthal:** 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.; Teva Pharmaceuticals. F. Consulting Fees (e.g., advisory boards); AbbVie.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.23/Z3

Topic: D.02. Somatosensation – Pain

Support: NCCIH
EMBO Postdoctoral Fellowship
Branco Weiss Fellowship

Title: Pain persists in mice lacking both Substance P and CGRPα signalling

Authors: ***D. I. MACDONALD**, M. JAYABALAN, J. SEAMAN, A. NICKOLLS, A. T. CHESLER;
NIH, Bethesda, MD

Abstract: Two of the most studied neuropeptides are Substance P and CGRPα. These molecules are highly expressed in pain-responsive neurons throughout the nervous system - both peripherally in nociceptors, and centrally in the spinal cord, brainstem and limbic system. Thus, it is widely held that both peptides must play important roles in modulating pain. Despite intense research over decades, Substance P receptor blockers failed to relieve pain in clinical trials. Although CGRPα monoclonal antibodies have proven effective for subsets of migraine patients,

their usefulness for other types of pain appears limited. We hypothesized that simultaneous inhibition of both Substance P and CGRPα signalling would be a useful strategy for treating pain. To test this, we generated *Tac1* and *Calca* double knockout (DKO) mice, resulting in complete loss of Substance P and CGRPα peptides throughout the nervous system. Behavioural testing revealed that DKO mice displayed largely intact responses to acute noxious stimuli of different modalities. To our surprise, chronic inflammatory and neuropathic pain was also unaffected by loss of the two peptides. Interestingly, and contrary to classical studies, DKO animals developed neurogenic inflammation. Substance P and CGRPα are therefore together not essential for the afferent transmission of pain and their combined inhibition is unlikely to produce analgesia.

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Poster

PSTR270. Nociceptors

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Program #/Poster #: PSTR270.24/Z4

Topic: D.02. Somatosensation – Pain

Support: MRC grant MR/V012738/1

Title: Exploring parameter space underlying somatic action potentials in models of small diameter dorsal root ganglion neurons

Authors: A. FELICIANO[1], N. GAMPER[2], ***D. JAFFE**[1];
[1]Univ. of Texas at San Antonio, San Antonio, TX; [2]Nikita Gamper, Univ. Leeds, Leeds, United Kingdom

Abstract: Action potential propagation along unmyelinated, C-fiber neurons may be regulated as they pass through dorsal root ganglia (DRG). The repertoire of axonal voltage-gated channels will be an important determinant of how their modulation will affect excitability and spike throughput. In particular, for spike propagation to be voltage-dependent, the density of high-threshold $Na_V1.8$ channels proximal to the T-junction is likely to be expressed at a lower density (compared with the soma) than TTX-sensitive (TTXs) channels. Here we examine the somatic conductance parameter space for several well-studied voltage-gated channels, to be used as a reference for studying how their differential expression between soma and axon affects spike propagation.
The model contains three groups of voltage-gated Na^+ conductances: TTX-sensitive channels (TTXs) channel and two TTX-resistant (TTXr) channels (1.8 and 1.9), along with two K_V channels (fast and slow). An initial model closely reproducing aspects of the somatic spike waveform and experimentally-measured Na_V currents underlying spikes used densities for TTXs and TTXr ($Na_V1.8$ and 1.9) of 1.4, 4.6, and 0.38 channels/μm^2, respectively. We then included a

high-voltage activated (HVA) voltage-gated Ca^{2+} channel and then systematically varied the 3 Na_V, 2 K_V, and Ca_V conductances 0.1-10X, and across three soma diameters (20, 26, and 32 μm) for a total of 46,872 configurations. Selecting for models based on action potential waveform and TTXs/TTXr current influx during the rising phase of 1/3 reduced the number of acceptable models to 2518. Distributions of TTXs and TTXr rising phase Na_V currents were multimodal and mean currents for higher-order modes were more than 3-fold larger than typically measured for somatic Na channels. Therefore, further selecting for the smaller mode of the TTXr current distribution resulted in 469 models. Finally, for models with 26 μm somatic diameters TTXs, $Na_V1.8$, and 1.9 densities were 0.8 ± 0.5, 4.4 ± 0.6, and 0.6 ± 1.0 channels/μm^2, respectively. The density of HVA Ca_V channels was 0.3 ± 0.2 channels/μm^2, while the total K_V density was 13.6 ± 12.5 channels/μm^2. From these somatic channel densities, we intend to explore how their differential axonal expression affects spike propagation through the DRG.

Disclosures: A. Feliciano: None. **N. Gamper:** None. **D. Jaffe:** None.

Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.25/Z5

Topic: D.02. Somatosensation – Pain

Support: NIH CA200263 (PMD)
NIH NS102432 (YIM, TLY)
NIH NS104769 (YIM, TLY)

Title: Apoa-i binding protein (aibp) regulates transient receptor potential vanilloid 1 (trpv1) activity in rat dorsal root ganglion neurons by disrupting the toll-like receptor 4 (tlr4) signaling pathway in cell membrane lipid rafts

Authors: Y. LI[1], ***M. L. UHELSKI**[3], K. E. MCDONOUGH[1], T. L. YAKSH[4], Y. MILLER[5], P. M. DOUGHERTY[2];
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Abstract: Paclitaxel is a frontline chemotherapeutic agent used to treat common solid tumors. This aggressive drug causes many side effects, including chemotherapy-induced peripheral neuropathy (CIPN). CIPN is chronic and causes severe neuropathic symptoms which can lead to dose reductions or premature termination of treatment. Neuropathic pain is known to involve pro-inflammatory immune responses, with CIPN exhibiting this same pathophysiological pathway. Toll-like receptors (TLRs) play an important role in the transition between inflammatory and chronic pain. Paclitaxel engages the TLR4 pathway, demonstrating an identical effect to pro-inflammatory agonist LPS. Transient receptor potential vanilloid subtype 1

(TRPV1), like TLR4, is upregulated in the dorsal root ganglia (DRG) of rats treated with paclitaxel, and TLR4 sensitizes TRPV1 in the presence of paclitaxel. Although we believe CIPN is related to the sensitization of peripheral sensory neurons, the cellular signaling pathways and other mediators need further study. Among the potential mediators is the increased presence of lipid rafts that form enhanced TLR4 signaling complexes. Lipid raft function can be explored using Apolipoprotein A-I binding protein (AIBP). AIBP is a protein that reduces lipid rafts, augments cholesterol efflux, and works in part by binding TLR4. Membrane cholesterol has previously been shown to directly influence cell surface expression of TRPV1 in rat DRG neurons, and depletion of cholesterol significantly reduced TRPV1 currents. In this study, TLR4 lipid raft modulation and its influence on nociceptor hyperexcitability and TRPV1 activity was examined in DRG neurons from wild-type and TLR4 knockout rats to determine unexplored mechanisms of CIPN and potential therapeutic pathways. We found that responses to capsaicin were reduced in DRG neurons from TLR4 knockout rats. Further, cholesterol depletion by TLR4-binding AIBP attenuated capsaicin responses in wild-type, but not TLR4 knockout rats. This effect was specific to TLR4, as non-specific cholesterol depletion by methyl-β-cyclodextrin attenuated capsaicin responses in both wild-type and TLR4 knockout rats. In DRG neurons from paclitaxel-treated wild-type rats, treatment with AIBP reduced the rate of spontaneous discharges and decreased responses to capsaicin. These results indicate that TLR4 signaling plays a role in the function of nociceptive properties in DRG neurons and that both TRPV1 and TLR4 signaling are modified in response to paclitaxel treatment. Future studies will explore the exact mechanisms leading to inhibition of action potential firing and capsaicin responses by AIBP.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.26/Z6

Topic: D.02. Somatosensation – Pain

Support: AFOSR grant 20RHCOR04

Title: Intranasal β-endorphin delivery for targeted antinociception in healthy male rats

Authors: *K. A. JONES[1,2], B. SHARMA[1,3], F. S. CURTNER[1,4], R. J. MOORE[1,4], H. C. MCCUBBINS[1,3], C. N. HATCHER-SOLIS[1];

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Abstract: The passage of molecules from the blood to the brain is restricted by the blood brain barrier (BBB) which regulates brain homeostasis and provides protection from toxic substances and pathogens. While the BBB is critical for neuronal function, it is also a major challenge for the delivery of bioactive molecules to the central nervous system for therapeutic applications. Intranasal administration can address this delivery obstacle as it provides a non-invasive route that bypasses the BBB for direct delivery of molecules to the brain. Here, we investigate the peptide β-endorphin (β-end) for antinociceptive effects and brain distribution after intranasal administration. The tail flick test assessed analgesia after intranasal delivery (n = 11-12) Rats which received intranasal β-end had reduced pain sensitivity as compared to control intranasal saline administration ($p<0.05$) while no significance difference was observed with an insulin control peptide ($p>0.05$). Rats were humanely euthanized immediately after behavior and tissue was collected for peptide detection by enzyme-linked immunosorbent assay (ELISA, n = 11-12). Efficiency of delivery was first confirmed with the control peptide insulin as intranasal insulin administration has been extensively characterized. Insulin significantly increased in all brain regions analyzed after intranasal insulin delivery as compared to intranasal saline administration ($p<0.01$). Intranasal β-end administration also significantly increased β-end concentrations in the brain ($p<0.05$), though there was no significant difference in β-end levels in the hypothalamus or cerebellum ($p>0.05$). While the peptide distribution patterns in the brain varied, the detection of increased β-end in the brain after intranasal administration supports the antinociceptive effects observed in the tail flick test. Future studies are aimed at improving the analgesic effect of intranasal β-end delivery by enhancing peptide bioavailability or targeting delivery to specific brain regions with various synthetic biology and nanotechnology approaches. All animal activities were approved under an IACUC protocol. This study was supported by AFOSR grant 20RHCOR04.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

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Program #/Poster #: PSTR270.27/Z7

Topic: D.02. Somatosensation – Pain

Support: NIH R01DA051876

Title: Inhibition of adenylyl cyclase and exchange protein activated by cAMP enhances potassium flux in primary and immortal neuronal cell cultures

Authors: *B. NELSON[1], C. HILL[1], A. H. KLEIN[2];
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Abstract: Understanding the mechanisms of opioid tolerance and withdrawal is critical to creating novel pain treatments. Acute administration of opioids activates *mu*-opioid receptors and decreases both cellular cAMP levels and nociceptor excitability. Yet during chronic opioid exposure, adenylyl cyclase (AC) activity is increased along with downstream targets including protein kinase A and exchange protein activated by cAMP (EPAC). The potential effectors of both AC and EPAC activity that may mediate neuronal activity are ion channels, including the ATP-sensitive potassium channels (K_{ATP}). The possible relationships between K_{ATP} channel function, AC and EPAC activity, and opioid signaling is still unknown. To address this gap in understanding, potassium flux (K flux) was measured in primary cultures of dorsal root ganglia (DRG) and SH-SY5Y neuroblastoma cells after inhibition of AC or EPAC. K flux responses to diazoxide, a K_{ATP} channel agonist, varied in mouse DRG and SH-SY5Y cells, therefore the cells with the highest response rate (100 and 200% from baseline, respectively) were compared amongst treatment groups. DRG were cultured from male and female C57Bl6 mice and DRG exposed to ST034307 (ST0, 2 uM), an AC1 inhibitor. DRG were labeled with Nissl Stain, isolectin B4 (IB4), and cholera B toxin (ChBTx) to categorize these cells. The number of DRG from female mice with a high K flux response after exposure to ST0 was 53% as compared to only 24% of neurons without exposure to ST0. Similarly, in male mice the number of DRG with high K flux increased from 41% for control conditions to 57% when exposed to ST0. Female and male mice have a similar distribution of IB4 and ChBTx labeling. All cell populations indicate an increase in the proportion of cells with high potassium flux after ST0 treatment, with the largest change occurring in unlabeled, or peptidergic C-type neurons with 41% and 19% more cells in the high range of K flux in females and males respectively. Similarly, the incidence of SH-SY5Y cells that with high responsiveness to diazoxide (K flux over 200% change compared to baseline) after morphine treatment and ST0 or HJC 0350 (1uM, 0.5uM), an EPAC2 specific inhibitor, was 31% and 40%, respectively compared to morphine treated cells (18%, 10uM for 72 hrs) and 27% in naive cells. SH-SY5Y cells treated with ST0 (1uM, 1 hour) demonstrated decreased K flux in morphine naive populations and increased K flux in morphine tolerant populations. This research illustrates that AC activity inhibits K flux in neuronal cells. Specifically, AC1 inhibition of K_{ATP} activity may sensitize nociceptive responses during chronic opioid conditions.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.28/Z8

Topic: D.03. Somatosensation – Touch

Support: MS Society of Canada MSSC-3761
CIHR Project Grant FRN162434

Title: Modulation of structural plasticity in mouse sensory neurons by innate immune factors is influences by electrophysiological activity and sex

Authors: T. N. FRIEDMAN[1], S. M. LAMOTHE[2], T. HAMMOND[2], H. T. KURATA[2], ***B. J. KERR**[3];
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Abstract: Sensory neurons display a remarkable degree of structural plasticity. While most critical during development, this process may also be recapitulated after injury or in the context of diseases that affect the nervous system. Neuronal plasticity is intricately linked to the activity of neuronal membranes. Voltage-gated potassium channels (Kvs) play a critical role in membrane hyperpolarization and repolarization after an action potential. The flow of potassium ions through Kv channels can directly impact the availability of intracellular calcium ions for crucial second messenger systems linked to neural plasticity. Thus, modulation of Kv channels can have profound effects on the plastic properties of neurons. There is strong evidence suggesting a link between sex and clinical neuropathic pain syndromes. Furthermore, studies using painful autoimmune models of inflammation have shown that female mice exhibit heightened immune responses, along with distinct changes in neural structures indicative of neural plasticity. Here, we aimed to investigate sex-specific changes in inflammation-evoked neural plasticity and how neural activity relates to this process.Whole DRG cultures were generated from male and female C57/BL6 mice. Neurons were cultured in the presences of conditioned media from bone marrow derived macrophages (BMDMs) that had been stimulated with either TNFα or IL-4. Neurons were stained with anti-beta III tubulin antibody to assess the extent of neurite outgrowth. In parallel, whole-cell patch clamp recordings were obtained from the neurons at acute (6-hour) and chronic (48-hour) time-points. To investigate the effects of modulating neuronal activity on neurite outgrowth, neurons were incubated with the Kv7 agonist retigabine (RTG) with the different macrophage conditioned media.Macrophage conditioned media (both TNF and IL-4 stimulated) resulted in increased neurite extension in female neurons, while male neurons only exhibited increased neurite outgrowth in response to conditioned media from IL-4 stimulated macrophages. Electrophysiology revealed an inverse correlation between heightened electrical activity and increased neurite extension. Interestingly, there was a dramatic reduction in spontaneous activity associated with the extent of neurite extension rather than the duration of culture. The application of RTG lead to an overall reduction in neurite outgrowth.Our findings suggest that neuronal plasticity is influenced by inflammatory mediators in a sex-specific manner and highlights the potential of using the Kv7 agonist retigabine to prevent aberrant neuronal plasticity under conditions of inflammation.

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Poster

PSTR270. Nociceptors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.29/Z9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: grants from NIH, NIGMS, 1R35 GM118182 to KJT
Grant from NIH R01GM132672 to SSC

Title: Regulation of neuronal HMGB1 release via an alpha7 nicotinic acetylcholine receptor-dependent mechanism

Authors: *H. YANG[1], S. PETRUZZELLI[2], A. TYNAN[3], M. BRINES[2], U. ANDERSSON[4], K. J. TRACEY[5], S. S. CHAVAN[5];
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Abstract: HMGB1 is a critical mediator of sterile injury- and infection-elicited inflammation and immunity. Our recent studies demonstrated that nociceptor HMGB1 is an essential component of the neuroinflammatory response to injury (Yang et al. PNAS 2021). Despite extensive evidence about the role of HMGB1 in inflammatory diseases, almost nothing is known on the regulation of HMGB1 release by neurons. Acetylcholine-mediated signaling via alpha7 nicotinic acetylcholine receptors (alpha7nAChR) inhibits HMGB1 release from immune cells and ameliorate multiple inflammatory conditions. Here, we reasoned that this cholinergic signaling via alpha7nAChR may play a role in regulating HMGB1 release by sensory neurons. To test, we developed an *in vitro* assay where dorsal root ganglion (DRG) sensory neurons expressing channelrhodopsin-2 (ChR2) release HMGB1 upon exposure to blue light (473 nm). Acetylcholine significantly reduces HMGB1 release by DRG nociceptors (HMGB1 levels in unstimulated = 3.4 $\pm$ 0.56 ng/ml; light-stimulated = 30.8 $\pm$ 2.2 ng/ml; light + 10 µM acetylcholine = 9.8 $\pm$ 3.5* ng/ml; *: $p<0.01$ *vs.* light-stimulated; n=5-6/group). Other cholinergic agonists, such as GTS-21 and carbachol, also suppress HMGB1 release by activated nociceptors. Acetylcholine also suppresses release of HMGB1 by pharmacologically activated sensory neurons. Stimulation of nociceptors with a TRPV1 agonist capsaicin resulted in the release of HMGB1 that is inhibited by acetylcholine (HMGB1 levels in capsaicin 5µM group = 20.3 $\pm$ 3.2; capsaicin 5µM + acetylcholine 10 µM = 8.3 $\pm$ 0.7* ng/ml; n=6; *: $p<0.01$). Since DRGs lack cholinergic innervation but express functional alpha7nAChR (Shelukhina et al, Brain Struct Funct, 2015), we reasoned that this receptor system could mediate the signals that inhibit neuronal HMGB1 release. Acetylcholine and GTS-21 fails to inhibit capsaicin-induced HMGB1 from DRGs from alpha7nAChR deficient mice (HMGB1 levels in capsaicin 5 µM group = 21.8 $\pm$ 4.5 ng/ml; capsaicin 5 µM + acetylcholine 10 µM = 23.5 $\pm$ 4.5 ng/ml; n=4; p=not significant). These results suggest that acetylcholine regulates HMGB1 release from nociceptors via alpha7nAChR-dependent cholinergic anti-inflammatory mechanism. (supported in part by grants from NIH, NIGMS, 1R35 GM118182 to KJT and R01GM132672 to SSC).

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Poster

PSTR271. Human Pain Imaging

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.01/Z10

Topic: D.02. Somatosensation – Pain

Support: NIH BRAIN Grant R01AT011447

Title: Characterization of vagal nerve pathways in visceral pain perception

Authors: *J. R. ROBBINS, Y.-T. CHENG, P. L. KATAYAMA, C. J. WOOLF;
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Abstract: Visceral pain (VP) is a prevalent symptom of multiple diseases and among the leading causes for seeking medical help. This referred pain is difficult to localize and even more difficult to treat. VP occurs when nociceptors of internal organs become activated, leading to a sensation of gastrointestinal (GI) discomfort. Current analgesics, particularly opioids, can worsen VP symptoms, especially GI-related symptoms, due to side-effects like constipation. Thus, characterization of the underlying circuitry for VP could inform better treatment strategies, and the vagal nerve (VN) pathway, which delivers parallel ascending signals with spinal projection pathways from the GI tract to the brain, serves as a potential target.
To characterize how ascending pathways encode GI pain, we used a chemogenetic approach to label and contextually activate visceral nociceptive neurons for behavioral paradigms. The parabrachial nucleus (PBN) is a known sensory relay for interoceptive inputs. Thus, we injected Cre-dependent AAV vectors to express activating-DREADDs in the PBN of FosCreERT2 mice. We then subjected the mice to 3% Dextran Sodium Sulfate (DSS) drinking solution to induce colonic inflammation. We injected 4-OHT to induce Cre to express the DREADD actuators. After this, we surgically ablated the VN pathway by a subdiaphragmatic dissection in a group of these mice (VGX). A second group of these mice underwent a SHAM procedure (SHAM), which is the same surgical procedure except the vagus nerve is left intact. As a further control, a third group underwent VN ablation before the DSS trapping. After a CNO injection to recall the visceral-pain associated neurons (VPANs), we performed a von Frey behavioral assay, which assessed the sensory dimension of VP through mechanical sensitivity testing, and a conditioned place aversion (CPA) assay, which assessed the affective and motivational dimension of pain by measuring the changes of their preference for darkness after pairing with VPAN reactivation over a two-day conditioning paradigm.
Our results show a non-significant difference between VGX and SHAM cohorts for the von Frey assay; however, we found a significant difference between the two cohorts for CPA. These findings demonstrate that the VN pathway is likely not directly involved in the sensory processing of GI VP, but rather mediates the affective dimension of VP perception. These findings can inform exploration of circuit-based treatments to modulate those VPANs that specifically govern the affective dimension of VP and direct attention to the spinal cord projection pathway as a potential arbiter of sensory VP perception.

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Poster

PSTR271. Human Pain Imaging

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Program #/Poster #: PSTR271.02/Z11

Topic: D.02. Somatosensation – Pain

Support: NIH/NINDS 1 R01 NS112356-01

Title: Alpha power is inversely correlated with intensity of pain ratings in healthy subjects

Authors: *S. M. MARGERISON[1], M. L. KEASER[5], B. W. STEWART[6], A. J. FURMAN[2], D. SPEIS[3], A. MAZAHERI[7], J. TEIXEIRA DA SILVA[4], D. A. SEMINOWICZ[8];
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Abstract: Alpha oscillations (8-12 hz) are the primary electrical activity recorded from the human brain. Prior studies have shown that contralateral sensory alpha power reduces during exposure to a noxious stimulus relative to baseline. Also, reductions in alpha power during anticipation of a painful stimulus are correlated with subjective pain intensity. However, the relationship between alpha power reductions during a painful stimulus and the subjective intensity of pain related to that stimulus is unknown. EEG data was collected during painful thermal stimulation applied to the left lower extremity in an MR environment. We then analyzed the data to determine the relationship between alpha power and pain intensity, hypothesizing that alpha power would correlate negatively with rated pain. Nine participants each experienced 50 total thermal stimuli over five runs. Participants were instructed to rate their perceived pain on a scale of 0-100 in 10-point increments. EEG data was filtered and re-referenced to the common average then decomposed with independent component analysis. The component displaying a peak in the alpha range and a topography most suggesting a source in the right primary sensory cortex (determined by comparison to a template) was determined for each participant and each run. A timeseries of alpha power values was calculated for each selected component. Average alpha power for each baseline period between thermal stimuli, and for each thermal stimulation was averaged to a single value and inserted into the timeseries. This was compared to pain ratings for individual trials. A negative correlation between alpha power and pain ratings was displayed during at least four of the five runs for seven of the nine participants assessed. Across all participants and runs, the average correlation was r= -0.162. Overall, our hypothesis was supported by this preliminary analysis despite the average correlation strength being low. Further analysis will determine brain regions displaying connectivity associated with both alpha power and pain ratings using fMRI data collected simultaneously with the EEG discussed above.

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Poster

PSTR271. Human Pain Imaging

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Program #/Poster #: PSTR271.03/Z12

Topic: D.02. Somatosensation – Pain

Support: NIH Grant EB026549
NIMH Grant MH076136

Title: Discrepant effects of predictive cues on pain-related brain responses and behavior

Authors: *H. JUNG[1], A. YAZDANPANAH[1], M. LINDQUIST[2], A. SOLTANI[1], T. WAGER[1]; [1]Dartmouth Col., Hanover, NH; [2]Johns Hopkins Univ., Baltimore, MD

Abstract: Expectations about possible outcomes modulate our everyday experience. Most studies have examined the effects of such expectations in separate domains; thus, it is currently unclear whether expectations in cognitive and affective domains are mediated through separate or shared neural substrates (domain-specific or domain-general). To address this question, we used a factorial design of 2 cue (high/low) x 3 stimulus intensity (high/med/low) across 3 tasks (somatic pain, vicarious pain, and cognitive effort) to investigate cue-expectancy effects across multiple domains. For each trial, participants were presented with a high or low cue ("cue"), subsequently reported their expectations for the upcoming stimulus intensity ("expectation rating") before they were administered blocks of thermal heat stimuli, vicarious videos of patients in pain, cognitive mental rotation images ("stimulus"), and finally reported their subjective ratings of intensity ("outcome rating").
Our behavioral results demonstrated a significant cue-expectancy effect, where higher cues were associated with higher outcome ratings. Surprisingly, we observed an opposite pattern for the neural results in the pain task. Using a multistudy-validated biomarker of pain (Neurological pain signature; NPS), we found that NPS-extracted brain activations were greater for low vs. high cues in the high stimulus intensity condition. Such patterns were indicative of a prediction error-like signal that motivated us to examine behavior using computational modeling. Thus, we fitted a reinforcement learning model of pain expectancy effects to the expectation and outcome ratings and found that despite a good fit of data, there was no significant relationship between the NPS-extracted brain activations and prediction errors. This suggests that the opposite cue-expectancy patterns in the pain-associated brain activation were not a by-product of prediction errors used for adjusting expectations over time.
Based on these results, we conclude that the current models may not be able to capture the interplay between behavioral ratings and stimulus-evoked nociceptive processes. Our next step is

to integrate a neural component into the reinforcement learning model to account for the divergent effects of brain and behavior. This could ultimately allow us to construct a holistic model for expectancy effects across somatic pain, vicarious pain, and cognitive effort and shed light on domain-generality/specificity of expectations.

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Poster

PSTR271. Human Pain Imaging

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Program #/Poster #: PSTR271.04/Z13

Topic: D.02. Somatosensation – Pain

Support: RO1AG076082

Title: Individual alpha frequency in individuals with chronic low back pain

Authors: *R. L. M. HO[1], J. PARK[1], W.-E. WANG[1], J. S. THOMAS[2], Y. CRUZ-ALMEIDA[1], S. COOMBES[1];
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Abstract: Individual alpha frequency (IAF) derived from resting state electroencephalography (EEG) has potential to become a clinically useful neural biomarker for pain. Data from several studies suggest IAF is lower in individuals with chronic pain when compared to healthy controls, yet a few studies, including one focused on individuals with chronic low back pain (cLBP) have failed to find the same results. While the study on individuals with cLBP found no differences in IAF between groups, psychological variables were correlated with IAF pointing towards psychological factors being a key variable in understanding the relationship between cLBP and IAF. Therefore, the purpose of our study was to investigate how subgrouping based on scores from psychological questionnaires affects measurement of IAF in a group of individuals with cLBP. We collected resting EEG and assessed IAF in a cohort of 70 individuals with cLBP, implemented three different IAF calculations, and separated cLBP subjects based on a psychological variables. We contribute two novel findings to the literature. First, separating our cLBP group based on a median split on Tampa Scale of Kinesiophobia and pain duration leads to a significant difference in all three IAF calculations. However, variables of pain intensity, pain interference, and pain related disability do not lead to differences in IAF. This finding suggests fear of movement and pain duration are keys to understanding differences in neural activity in individuals with cLBP. Second, PCA analysis found a component comprised of pain intensity, disability, and fear of movement and this component was predictive of IAF.

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Poster

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Topic: D.02. Somatosensation – Pain

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Mayday Fund
Cathedral Fund

Title: Altered Resting State Functional Connectivity following Oral Morphine: A Functional Near-infrared Spectroscopy Study

Authors: *K. KARUNAKARAN[1], K. PENG[2], M. YUCEL[3], E. A. BITTNER[5], R. EDWARDS[7], L. BECERRA[8], D. A. BOAS[4], D. BORSOOK[6];
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Abstract: The use of brain measures to evaluate therapeutic effects has recently included functional Near Infrared Spectroscopy (fNIRS). Few studies using this domain have included drugs such as analgesics. As such the evolution of the use of fNIRS, because of its portability, cost and potential use in the clinic, has some significant advantages over other modalities such as EEG and fMRI. Here we evaluate the effects of an oral analgesic, immediate release morphine (10mg) tablets, on the resting state functional connectivity (RSFC) of the cortex using fNIRS. The cohort was previously evaluated for the effects of oral morphine on evoked cortical response to noxious stimuli. Each subject acted as their own control in a double blind-placebo controlled study. Peak plasma concentrations after oral immediate release morphine (Tmax) occurs at approximately 1 hour. Based on the onset and offset of morphine (Tmax=60 minutes), the study for drug and placebo each took place on separate sessions for a duration of 90 minutes. Using a repeated measures ANOVA at FDR-$p<0.05$, our results indicate (1) a decrease in the RSFC between right medial frontopolar cortex and right primary somatosensory cortex at both 30-mins and 60-mins after ingestion, recovering to the levels of placebo group at 90-mins; and (2) increase in RSFC within the prefrontal cortex, specifically between lateral and medial frontopolar cortex immediately after morphine ingestion at 30-mins that gradually reduced at 60- and 90-mins post morphine. This study is amongst the first to report that the system can detect alterations in brain functional connectivity in response to a well-known analgesic, morphine. Such evaluations allow for measure of drug effects on brain systems that may in future be used in clinical studies to provide an objective marker.

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Poster

PSTR271. Human Pain Imaging

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Program #/Poster #: PSTR271.06/Z15

Topic: D.02. Somatosensation – Pain

Support: NCCIH P01AT006651
NIDA T32DA035165
NIDA K24DA029262

Title: Assessing sex differences in the neural activity of chronic pain patients practicing emotion regulation techniques while receiving painful thermal stimulation

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Abstract: Globally, chronic pain is the number one reason individuals seek medical care. However, females are more likely to have chronic pain, more severe pain, and receive less treatment. Many reasons underly sex differences in pain (e.g., hormonal differences), and recent work has identified sex differences in neural activity and network organization of those with chronic pain. Whether these alterations in brain activity impact the effectiveness or how cognitive and top-down processes alter pain perception is still understudied. Here, we tested two emotion regulation (ER) techniques, reappraisal (termed reframing) and acceptance (termed observation) in their effectiveness in decreasing pain during an acute pain paradigm by sex. 172 chronic low back pain participants (94 males) had their brain activity measured during four conditions: no pain, pain with no regulation, pain with observation, and pain with reframing. Each pain stimulus was individually tailored and after each trial, participants rated pain intensity and unpleasantness. We noted no behavioral differences by sex, via two-sample t-tests, in calibrated temperature ($p = .82$), pain intensity ($p > .90$), or unpleasantness ($p > 0.70$). We noted a marginal difference by sex for age ($p = .08$), thus we included age as a covariate in our imaging analysis. For our neuroimaging data, first level images were processed using FEAT 6.0 and submitted for second-level analyses. Our contrasts of interest included No Regulation vs. No Pain, Observe vs. No Pain, and Reframe vs. No Pain separately and for Males vs Females. We looked at active brain regions with a threshold set at $z >= 2.3$ with a corrected cluster significance level of $p < .05$. We noted females had greater neural activity compared to males in the superior temporal gyrus ($z = 4.26$, $p < .001$) and cuneus ($z = 3.36$, $p = 002$) during no regulation vs. no pain, greater anterior cingulate cortex (ACC; $z = 4.71$, $p < .001$) activity during

observation vs. no pain, and greater medial orbitofrontal cortex (mOFC; z = 3.85, p <. 001) activity during reframing vs. no pain. Males had greater neural activity in the precuneus compared to females during both no regulation (z = 4.51, p < .001) and observation (z = 4.36, p = .01) vs. no pain. Our results suggest female chronic pain patients engage greater recruitment of the ACC and mOFC, both implicated in descending pain modulation, during ER. Our behavioral results suggest a significant decrease in pain during both ER conditions (p < .001) for both sexes. Interestingly, our behavioral results do not suggest sex differences in the effectiveness of ER, but neuroimaging reveals potential sex differences in the neural mechanisms underlying pain reduction with ER.

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Poster

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Program #/Poster #: PSTR271.07/Z16

Topic: D.02. Somatosensation – Pain

Support: R01 NS112356
R01 AT007176

Title: Altered claustrum and cognitive task network activity in chronic pain

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Abstract: The claustrum was recently hypothesized to support the initiation of cognitive control network activity, and multiple studies suggest pain is a cognitive load. We therefore used multiple human fMRI datasets, including data from healthy controls and chronic pain patients, to measure claustrum and cognitive task associated network activity in response to cognitive task, experimental pain, and pain anticipation conditions. Significant signal increases were detected in bilateral claustrum to experimental pain in healthy controls, and the introduction of a pain-predictive cue resulted in a shift of claustrum responses from pain to the preceding cue. Control protocols allowed extraction of claustrum BOLD signal distinct from neighboring structures, with claustrum activation confirmed as significantly different than insular cortex and anterior insula activation in multiple conditions. Significant bilateral claustrum responses to pain were also detected in chronic pain patients, with the right claustrum exhibiting greater activation at pain onset in patients than controls. Significantly different multivariate patterns of cognitive task

associated activity were also detected between groups, with patients exhibiting multiple clusters of greater task associated activity than controls. A region associated with cognitive task processing exclusively in patients was identified as a pain-responsive region in healthy controls, and signal changes in this region and right claustrum were correlated across experimental conditions, suggesting a link between claustrum and cognitive task network alterations in chronic pain.

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Poster

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Topic: D.02. Somatosensation – Pain

Support: DOD Grant SC190134
NIH award 1 S10 OD025085

Title: Functional MRI Assessment of Plasticity within Spinal Cord Circuits in Rats with Neuropathic Pain after Spinal Cord Injury

Authors: *X. ZHANG[1,2], C. MU[1,2], A. MISHRA[1,3], F. WANG[1,3], P.-F. YANG[1,3], J. C. GORE[1,2,3], L. CHEN[1,2,3];
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Abstract: Neuropathic pain is highly prevalent in patients with spinal cord injury (SCI) and is often resistant to treatments. We previously demonstrated that high-resolution fMRI showed localized responses to tactile and heat stimuli in the deeper and superficial laminae of the spinal cord dorsal horn. This study aims to use fMRI to (1) demonstrate nociceptive heat stimulation-evoked activations in spinal grey matter horns/zones, (2) measure resting state functional connectivity (rsFC) within the network of nociceptive-processing horns, and (3) quantify behavioral responses to somatic and thermal pain stimuli in a rat T13 contusion spinal cord injury model. Eight rats were studied longitudinally and were scanned before and after an injury at weeks 1, 4, and 8 under anesthesia. Images were acquired during both a resting state and after the application of 47.5 °C noxious heat stimulation to the left hind paw. FMRI activation patterns within and across segments were mapped and we measured the strength of rsFC between spinal horns. Weekly behavioral tests, including Von Frey tactile filament, hot plate, and Hargreaves tests, were also conducted. All rats exhibited neuropathic pain behavior. Our results revealed widespread heat stimulus-evoked fMRI activation foci in the left dorsal horn across multiple segments above and below the injury level within one week post-injury. Starting from week 4 post-injury, activation location shifted. Following the injury, the rsFC between spinal horns

decreased immediately and began to recover after week 4 post-injury. Parallel behavioral testing revealed that the mechanical detection threshold for the Von Frey test was significantly increased after the injury and gradually returned to baseline starting from week 3 post-injury. The paw withdrawal latency for the Hargreaves test shortened, indicating thermal hyperalgesia post-injury. Our results showed a dynamic shift in activation region to heat stimulus post-injury over time, with horn-to-horn connectivity recovering by week 4 post-injury while the mechanical detection thresholds recovered by week 3. In summary, this study found correlated temporal relationships between plastic changes in segmental-wise gray matter heat responses and inter-horn connectivity and the development of below-level neuropathic pain behavior. These results provide novel insights into spinal circuit contributions to neuropathic pain development, suggesting the dorsal horns play a leading role.

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Poster

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Program #/Poster #: PSTR271.09/Z18

Topic: D.02. Somatosensation – Pain

Support: Department of Neural and Pain Sciences Research Fund

Title: Effects of Environmental Enrichment on Visceral Sensitivity and Brain Connectivity in a Mouse Model of Chronic Overlapping Pain Conditions

Authors: *M. L. KEASER[1], S. HANSON[1], A. J. SCOTT[2], R. J. TRAUB[1,3], J. T. DA SILVA[1,3]; [1]Neural and Pain Sci., [2]Dept. of Microbial Pathogenesis, Univ. of Maryland, Baltimore Sch. of Dent., Baltimore, MD; [3]Ctr. to Advanced Chronic Pain Res., Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: Temporomandibular disorder (TMD) and irritable bowel syndrome (IBS) are two chronic overlapping pain conditions (COPCs) that present with significant comorbidity. Both conditions are more prevalent in women and are exacerbated by stress. While peripheral mechanisms might contribute to pain hypersensitivity for each individual condition, mechanisms underlying the comorbidity are poorly understood, complicating pain management. It has been suggested that pain amplification in COPCs is the result of dysfunctional CNS pain processing caused by altered connectivity among several brain regions, including the insula. Nonpharmacological therapies such as Environmental Enrichment (EE) have been shown to reduce pain- and anxiety-like behaviors, enhance learning and memory, and induce neural plasticity. We have developed a mouse model of comorbid pain hypersensitivity (CPH: stress during preexisting orofacial pain, Complete Freund's Adjuvant (CFA) induced masseter muscle inflammation) and examined the effects of EE on behavioral and brain connectivity changes

induced by this model. Eighteen female mice underwent resting-state fMRI scans. The 18 mice were divided into 3 groups: 6 CPH + EE, 6 CPH only, and 6 naive mice. Referred pain (visceral pain correlate) was measured as the increase in responsiveness to von Frey stimulation of the lower abdomen above baseline mechanosensitivity following inflammation and stress. A seed-based correlation analysis approach was used to determine changes in insula connectivity to the whole brain in relation to CPH and how EE affects, if at all, this relationship. CPH increased referred pain in female mice for at least 4 weeks. EE blocked the referred pain development. Contrast map results ($p < 0.05$) show mice placed in an enriched environment exhibited significantly lower insula connectivity to the following regions compared to CPH mice without EE: Claustrum, Caudoputamen, Central medial nucleus of the thalamus, Central amygdalar nucleus, medial part (Allen Brain Atlas nomenclature). In addition, CPH mice with EE show a trend of increased connectivity between insula and periaqueductal gray, which is similarly seen in naive mice compared to CPH group. These results demonstrate that EE can reduce referred pain and functional connectivity of areas involved in pain and stress processing, and may be strengthening the impaired endogenous pain inhibitory system seen in comorbid pain conditions. Further experiments are currently being done to fully investigate the effects of EE on comorbid pain conditions and potential sex differences.

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Poster

PSTR271. Human Pain Imaging

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Program #/Poster #: PSTR271.10/Z19

Topic: D.02. Somatosensation – Pain

Title: Intrinsic anterior insula activity distinguishes individuals with rotator cuff tendinopathy from healthy, matched controls

Authors: *M. HEINDEL[1], J. J. KUTCH[2], L. A. MICHENER[2];
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Abstract: Title: Intrinsic Anterior Insula Activity Distinguishes Individuals with Rotator Cuff Tendinopathy from Healthy Controls
Authors: Heindel MD, Kutch JJ, Michener LA; Biokinesiology, University of Southern California
Disclosures: None
Motivation/problem statement: Shoulder pain affects up to 25% of the general population, and rotator cuff tendinopathy (RCtend) is the most common diagnosis. Unfortunately, 40-50% of those with RCtend develop recurrent or chronic pain. Nociceptive input from the tendon to the central nervous system has been considered the primary mechanism of pain. However, recent evidence suggests central nervous system dysfunction underlies the development and progression

of RCtend, specifically increased centrally-defined pain sensitivity. However, identified central mechanisms of RC tendinopathy are sparse, and there have been no direct measures of intrinsic brain activity. Therefore, we hypothesized intrinsic brain activity would differentiate those with RCtend from healthy controls (HC).
Methods/Approach: Cohort of 19 individuals with right-sided RCtend and 19 HC, matched for age, sex, and body mass index, underwent resting-state fMRI. Preprocessing was completed with *fMRIPrep v 20.0.7.* Images were smoothed, bandpass filtered for fractionated amplitude of low frequency fluctuation content (fALFF) in the slow-5 band (0.01 to 0.027), and 6 acompcor confounds of no interest were removed using *Analysis of Functional Neuroimages 3dTProject.* A whole-brain group-level analysis was performed with a cluster-wise threshold of $z > 2.3$ and cluster significance threshold of $p < 0.05$ with *Functional MRI of the Brain Software Library* (FSL) v.6. An independent t-test was used to compare groups (RCtend, HC) with pain in the scanner as a demeaned covariate.
Results: The group with RCtend had greater activity than HC in the right anterior insula (406 voxels, $p < 0.001$).
Conclusion: There was greater resting-state activity in those with RCtend than HC. Therefore, intrinsic anterior insula activity may be useful to distinguish those with RCtend from HC. The anterior insula is involved in both pain processing and the unpleasant experience associated with pain. Therefore, the centrally-defined pain sensitivity may relate to dysfunction of the anterior insula. Longitudinal research and validation on larger datasets is needed to characterize the relationship of anterior insula activity and centrally-defined pain sensitivity.

Disclosures: M. Heindel: None. **J.J. Kutch:** None. **L.A. Michener:** None.

Poster

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Topic: D.02. Somatosensation – Pain

Support: NIDA R01 DA046064
NIBIB R01 EB026549
NIMH 3R01 MH076136

Title: A resting state connectivity functional alignment model for pain prediction

Authors: *B. PETRE[1], M. CEKO[3], N. P. FRIEDMAN[4], M. C. KELLER[4], M. A. LINDQUIST[5], T. D. WAGER[2];
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Abstract: Anatomical landmarks are used to establish functional correspondences for population level studies of the brain, but interindividual functional variability is not fully captured by

anatomical alignment. To resolve potential idiosyncratic functional topographies and tuning profiles we develop and compare two high quality templates of a functional connectome using resting state data from the human connectome project (HCP, N=333, 1 hour/participant). HCP participants are prealigned using multimodal surface matching (MSM) warps, but we further refine this. First we generate a diffeomorphic reference template by averaging MSM aligned connectomes across participants. Second we hyperalign individuals' voxel-level tuning curves to the common template using high dimensional orthogonal transformations. Two constraints regularize the latter. We perform alignment within coarse scale regional parcellations of the cortical surface or volumetric structures, and also incorporate a novel subspace projection to ensure regional mean invariance. These templates represent different hypotheses of interindividual functional correspondence, either a common coarse topography or a shared set of higher-dimensional finer-grained tuning profiles, respectively. We test these templates using data from a separate study of multimodal pain behavior (N=150). Using five minutes of resting state data we compute diffeomorphic alignments of connectomes to the first template and fit a shared response model to project tuning curves to the second template. We then compare between subject correlations (BSC) in pain evoked topographies, and out-of-subject discrimination of experimental conditions and pain prediction. Diffeomorphic alignment significantly increases BSCs when considering the entire brain ($t=121.8$, $p < 10e-5$, ~5% increase in variance explained), or only considering within region BSC ($t = 98.8$, $p < 10e-5$, 23.2% increase). Subsequent shared response model hyperalignment decreases overall BSC, especially in areas along the somatosensory strip (FDR $q=0.05$) and cerebellum. Paradoxically, out of participant decoding of pain intensity and modality improves after hyperalignment (Mean accuracy heat vs. pressure = 0.766 vs. 0.789, mean predicted pain vs. observed pain within participant $r2 = 0.218$ vs. 0.247). These preliminary results suggest different models of functional correspondence may be appropriate for different brain areas, and establish a first benchmark for interpretable functional template construction and implementation.

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Poster

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Program #/Poster #: PSTR271.12/Z21

Topic: D.02. Somatosensation – Pain

Support: UVA Brain Institute
UVA Neurosurgery

Title: Contactless cutaneous Laser reliably induced Temporal Summation of Pain - a Comparison between Body Sites and Sex

Authors: *X. ZHANG, D. WANG, W. CARTER, A. TRINH, S. MOOSA, W. J. ELIAS, C.-C. LIU;
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Abstract: Temporal summation of pain (TSP) is an endogenous pain facilitation phenomenon characterized by elevated pain intensity to a series of identical painful stimuli. Greater TSP has been linked to central sensitization and higher risks for chronic pain development. However, current literature reported inconsistent results for sex and body site differences on TSP responses. One possible limitation in previous studies was the use of contact thermode which inevitably activate low-threshold mechanoreceptors that may reduce mask painful sensation during heat pain delivery. In the present study, we used contactless painful laser stimulation for heat pain delivery to test the hypothesis that no significant difference in TSP responses between female and male subjects across body sites in healthy subjects. A Nd:YAP laser stimulator (wavelength 1.34μm, beam diameter 8mm, pulse duration 4ms) was used for contactless heat pain delivery. During TSP induction, painful laser stimulations were delivered in triplet fashion (i.e. S1, S2, S3 with a fixed inter-stimulus interval of 1.5s) with a constant stimulus intensity (40-50/100 pain intensity adjusted at the baseline), and a random inter-triplet interval between 10-30s. Stimulus related EEG recordings (1000Hz sampling rate, 0.1-25Hz bandpass) were extracted into -0.1 to 1.4s for laser evoked potentials (LEPs) analysis. Twenty-six healthy subjects were enrolled (25.5 ± 2.3 yrs, 11 female) to the present study. Subjects were instructed to attend to the laser stimulations and report pain intensity for each stimulus using a 0-100 visual analogue scale. TSP responses were quantified as the increased pain from S1 to S3, and normalized by the S1 (i.e. TSP = (S3-S1)/S1). We found that the TSP were induced in all subjects ($p < 0.01$). No significant TSP difference was found across body sites (hand, leg, and back), indicating that TSP is a centrally mediated phenomenon. Female subjects showed greater TSP than male subjects ($p < 0.05$). Furthermore, significant correlations were found between LEP amplitudes and TSP responses ($p<0.01$, Spearman rank correlation). In conclusion, our preliminary findings demonstrated comparable TSP across body sites, and stronger TSP responses were found in female subjects.

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Poster

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Program #/Poster #: PSTR271.13/Z22

Topic: D.02. Somatosensation – Pain

Title: Functionally mapping the transition from acute to chronic pain using awake rs-fMRI & Next-Generation Behavioral Sequencing

Authors: *A. Z. JHUMKA, D. LICHTMAN, A. A. LAWEN, I. KAHN, I. ABDUS-SABOOR; Columbia Univ., New-York, NY

Abstract: Chronic pain is a heavily debilitating disease affecting more than 1.5 billion people worldwide. Epidemiological and functional imaging studies suggest a bidirectional relationship between chronic pain and mental health disorders, which can partially be explained by shared neural mechanisms. Current pain neuroimaging studies present tremendous potential in terms of translational diagnostic, prognostic and or treatment-response tools. However, many technical obstacles persist. Indeed, the variability across chronic pain patients and conditions makes it challenging to understand functional brain dynamic alterations supporting pain chronification. While pain duration varies according to the initial cause of tissue injury, there is no rigorously controlled study establishing both semiology- and etiology-specific dynamic brain signatures for the transition from acute to chronic pain. In other words, can we functionally map the transition from acute to chronic pain and can we target such alterations to abort or reverse pain chronification mechanisms? In line with this, most preclinical pain neuroimaging studies are performed on anesthetized laboratory animals, which is a confound considering the analgesic effect of anesthetics. Furthermore, pain, *stricto sensu*, is challenging to measure in animals because they cannot verbally communicate with experimenters. In line with this, indirect measurements of pain in animals have long relied on the quantification of spontaneous nocifensive behavioral bouts, evoked withdrawal reflexes, touch or temperature avoidance, etc. While these readouts are informative on animals' sensitivity, such assays bear a number of caveats such as experimenter-induced variations and or bias, sensitization or habituation of animals to given stimuli, etc. Such caveats render correlations between chronic pain behavior and real-time brain activity challenging. Here we present a unique and unprecedented pipeline based on next-generation behavioral sequencing and awake resting-state fMRI in head-fixed mice, to functionally map the transition from acute to chronic pain in real time by correlating functional brain and behavioral signatures according to the etiology of the pain.

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Poster

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Program #/Poster #: PSTR271.14/Z23

Topic: D.02. Somatosensation – Pain

Support: KBI Postdoctoral Fellowship Award

Title: The impact of trigeminal neuralgia pain on the hippocampus and its major efferent pathway

Authors: *P. SRISAIKAEW[1], T. LATYPOV[3], D. JOERGENS[1], W. WANG[1], A. NOORANI[3], S. HANYCZ[5], M. WALKER[2], M. HODAIE[4,1];
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Abstract: Trigeminal neuralgia (TN) is a severe chronic neuropathic pain disorder with intense shock-like pain in distributions of the trigeminal nerve branches and over 70% of patients experienced memory difficulties. Evidence suggests the hippocampus (HPC) and its major efferent pathway, fornix (Fx), are not only involved in memory but also involved in pain processing and pain modulation. Abnormalities of the HPC and the Fx have been reported in chronic pain patients. However, how these structural abnormalities change before and after surgery in TN patients remains poorly understood. We aimed to investigate the changes in the HPC and Fx and their potential resolution following TN pain relief. 3T T1w and DWI images from 54 TN participants (pre-/6 months postsurgical) and 54 age-/sex-matched healthy controls were recruited and analyzed. FreesSurfer was used to perform HPC subfields volumetric segmentation using T1w data. DWI data were pre-processed and all DTI values (fractional anisotropy, FA; and axial, mean, and radial diffusivities, AD, MD, and RD) of the Fx were obtained. All statistical analysis was performed using Python. A significant statistical level was set at $p<0.05$ and multiple comparisons correlation was done. The reduction of the HPC volume and Fx integrity was found in TN patients at both time points compared to controls ($p<0.001$), over and above the influence of age and sex. HPC subfields volumes (CA4 and dentate gyrus) were significantly increased following the pain relief, however, abnormalities found in the Fx did not normalize after surgery. Pain-related functional hemispheric asymmetry was found in the HPC normalization pattern toward the right hemisphere - this effect was more robust in patients who experienced pain relief after surgery. A significant sex difference was found only in the Fx at the postsurgical timepoint. This suggests that males and females TN may be responding to the treatment differently. Our findings revealed a significant impact of pain on both macro- (HPC volume) and micro-structural (Fx integrity) levels in the limbic circuitry. However, a discordant normalization is observed only in the macrostructure (HPC volume) and the functional asymmetry was found toward the right hippocampus. These findings advance our understanding of CNS-related dynamic abnormalities in chronic neuropathic pain, particularly in the limbic structures.

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Poster

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Program #/Poster #: PSTR271.15/Z24

Topic: D.02. Somatosensation – Pain

Support: R21DA047673

Title: Pain embodiment measures and related disruptions in the anterior cingulate cortex are associated with increased risk for aberrant opioid-related behavior in chronic pain patients

Authors: *K. SHAH, J. MA, *J. ROGOWSKA, M. LEGARRETA, E. MCGLADE, P. RENSHAW, D. YURGELUN-TODD;
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Abstract: Pain embodiment is a form of maladaptive body awareness whereby dysfunctional integration of painful sensations into the assessment of bodily states, such as the tendency to apprise sensations as a threat to bodily integrity, changes the way the body experiences pain. This study examines how chronic pain embodiment and associated changes within the anterior cingulate cortex (ACC) relate to the risk for aberrant opioid-related behaviors (AORB). Participants were 23 adults (13M/10F) with chronic musculoskeletal or primary pain for >3 months and free from substance abuse for >60 days (mean age: 34.9 years, sd 6.0; mean duration of pain: 11.0 years, sd: 6.6). The Multidimensional Assessment of Interoceptive Awareness evaluated pain embodiment. The Current Opioid Misuse Measure (COMM) quantified current AORB risk. Low-and high-risk stratification for the COMM was determined using the clinical cutoff of ≥9. Neuroimaging consisted of a resting-state BOLD MRI scan and ^{1}H magnetic resonance spectroscopic data acquired in the ACC. T-tests were used to measure differences in pain embodiment measures and ACC metabolite concentrations between low- and high-risk COMM groups. Multiple regression was performed with pain embodiment measures against the default mode network (DMN) using a seed in the posterior cingulate cortex (FWE-corrected, $p<0.005$, $k>20$). Pearson correlations were used to examine the relationships between embodiment measures and ACC metabolite concentrations. Participants with high-risk COMM scores report a higher tendency to distract from painful sensations, a higher tendency to worry about painful sensations, and a decreased ability to regulate pain-related distress. Worrying about painful sensations associated with increased DMN connectivity with the right ACC and left frontal superior cortex ($p=0.007$). ACC Glx (combined glutamate and glutamine) negatively correlates with the tendency not to distract from painful sensations ($r=-.55$), the tendency not to worry about painful sensations ($r=-.46$), and the ability to regulate attention to body sensations ($r=-0.49$). Participants with high-risk COMM scores exhibit higher concentrations of ACC Glx. Overall, increased pain embodiment in chronic pain patients is associated with increased ACC Glx, increased DMN connectivity to the ACC, and increased risk of AORB. The ability to self-regulate distress and attention to bodily sensations may be protective factors against developing opioid misuse behaviors. This study highlights the importance of pain embodiment as it relates to changes in the ACC and chronic pain behaviors such as risk for aberrant opioid-related drug misuse.

Disclosures: K. Shah: None. **J. Ma:** None. **J. Rogowska:** None. **M. Legarreta:** None. **E. McGlade:** None. **P. Renshaw:** None. **D. Yurgelun-Todd:** None.

Poster

PSTR271. Human Pain Imaging

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.16/Z25

Topic: D.02. Somatosensation – Pain

Support: NIH Grant K01HD092612

Title: Structural sensorimotor adaptations in young adults with low back pain.

Authors: *J. ARMOUR SMITH[1], **I. CHRISMAN**[2], R. TAIN[3], K. G. SHARP[4], L. M. GLYNN[2], L. R. VAN DILLEN[5], J. V. JACOBS[6], S. C. CRAMER[7];
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Abstract: Background. Chronic low back pain (CLBP) is now the largest cause of disability worldwide. There is increasing evidence for region-specific patterns of structural brain adaptation in individuals with CLBP. Most studies have investigated middle-aged adults and typically demonstrate decreased grey matter density in regions associated with pain processing. It is not clear if structural adaptations are evident early in the lifespan in individuals with CLBP in regions associated with sensorimotor function. The purpose of the study was to compare sensorimotor gray matter density in young adults with a history of CLBP compared with back-healthy controls. Methods. Fifty-three young adults with a greater than 1-year history of CLBP (average age 21.9 ± 3.1 years) and 29 young adults with no history of LBP (average age 23.7 ± 4.0 years) participated. Clinical characteristics of the LBP group were quantified with measures of pain duration, intensity, and impact as well as pain-related fear, disability and typical physical activity. Gray matter density was quantified using voxel-based morphometry. Whole brain and sensorimotor region of interest (ROI) comparisons between groups were made after covarying for age and total intracranial volume. ROIs were determined *a priori.* The association between clinical characteristics and average gray matter density in sensorimotor ROIs were explored using Pearson's correlation coefficients. Results. Individuals with LBP reported an average duration of pain of 4.8 (± 2.2) years and average pain intensity of 5.0/10. Whole brain analyses indicated significantly greater gray matter density in the LBP group in the right primary somatosensory cortex, right superior parietal lobule, and right/left inferior parietal lobule (all comparisons $p < 0.001$ uncorrected). The LBP group had less gray matter density in the right caudate nucleus ($p < 0.001$ uncorrected). ROI analysis showed that the LBP group had greater gray matter density in the right primary somatosensory cortex and right primary motor cortex ($p < 0.05$ FWE corrected for both comparisons). No areas of decreased gray matter density in the LBP group survived FWE correction. There were no significant linear associations between clinical characteristics and average gray matter density in the selected ROIs.Conclusion.We demonstrate that in young adults, persistent musculoskeletal pain is linked with structural neuroplasticity in regions associated with sensory processing and motor control. Increased grey matter density early in the lifespan of individuals with CLBP may reflect an adaptation to ongoing nociceptive input.

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Poster

PSTR271. Human Pain Imaging

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.17/Z26

Topic: D.02. Somatosensation – Pain

Support: F31NS126012
1P50DA044121

Title: Nucleus Accumbens Valence Processing During Offset Analgesia

Authors: *A. D. VIGOTSKY[1], R. JABAKHANJI[1], L. HUANG[2], P. BRANCO[3], M. BALIKI[1], A. APKARIAN[1];
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Abstract: Pain is not a static function of a noxious stimulus; rather, it is a time-evolving experience whose history-dependence arises from the complex interaction of multiple circuits. This is especially apparent in offset analgesia, a pain psychophysical phenomenon characterized by disproportionately large decreases in pain following a small decrease in the intensity of a noxious stimulus. Offset analgesia's dynamic uncoupling of the stimulus from the sensation has intrigued the field of pain research since its discovery over a decade ago, but its mechanisms have remained elusive. Pharmacological studies have ruled out opioidergic (e.g., descending inhibitory circuits) and NMDAergic circuits (e.g., diffuse noxious inhibitory control circuits). In this work, we build on our previous work proposing that offset analgesia may arise from mesolimbic dopamine circuits. We combined psychophysics, modeling, and functional magnetic resonance imaging (fMRI) to study how local dopamine circuit dynamics (nucleus accumbens, NAc) relate to offset analgesia. Specifically, we investigated how latent dopamine neuron dynamics, which capture the time course of offset analgesia, map onto NAc activity. We recruited fourteen healthy individuals (10 M, 4 F) to participate in this study. We collected fMRI (3T, 2×2×2 mm^2, multiband 4, multi-echo 4, 64-channel head/neck coil) while applying an offset analgesia stimulus train to the participants' volar forearms. We fit a mesolimbic valence competition model to the participants' pain ratings. Our model uses coupled first-order differential equations and posits that rewarding and aversive dopamine neuron subpopulations compete with one another, such that decreases in the intensity of the noxious stimulus activate reward circuits, which inhibit aversion circuits, thereby promoting algesia. We then used the latent reward and aversion time series from the model in a general linear model of NAc activity. Preliminary results indicated disparate positive and negative valence-related NAc activity, which was spatially heterogeneous. These preliminary findings are consistent with the dopaminergic hypothesis of offset analgesia and the spatial arrangement of dopamine neuron subtypes.

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Poster

PSTR271. Human Pain Imaging

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.18/Z27

Topic: D.02. Somatosensation – Pain

Support: ZIA-AT00030

Title: Domain-general and domain-specific activations of expectancy-based pain modulation as compared to aversive and pleasant tastes

Authors: Y. ZHAO[1], I.-S. LEE[4], Q. YU[1], M. ROSE-MCCANDLISH[1], D. MISCHKOWSKI[5], J. AVERY[2], J. INGEHOLM[2], *L. ATLAS[3];
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Abstract: The specificity of pain perception remains controversial. Previous studies have proposed a pain-specific brain matrix and specific neural patterns, such as the neurologic pain signature (NPS; Wager et al., 2013) and the stimulus intensity independent pain signature (SIIPS; Woo et al., 2017). However, activation in these brain networks has been found to overlap with other salient experiences and a general negative affect pattern (Čeko et al., 2022). The orbitofrontal cortex (OFC) has been implicated in value-based learning across various domains, including pain. The anterior insula has been found to play a role in expectation modulation, with a particular subregion exclusively influenced by expectancy of pain rather than other aversive events (Sharvit et al., 2019). However, the expectation effect and underlying neural mechanisms across pain and both aversive and pleasant sensations have not yet been directly investigated. In this study, we compared pain perception with perception of both unpleasant and pleasant tastes (i.e., salt and sugar), to isolate the distinctive and common modulatory effects of expectation on pain and tastes. We randomly assigned sixty participants to receive either heat stimulation, liquid salt, or liquid sugar during fMRI scanning (n = 20 per group). During conditioning, visual cues were paired with high-intensity (high cue) or low-intensity (low cue) stimulation. Each cue was then equally likely to be followed by its conditioned intensity or a medium intensity stimulus. Intensity and valence were rated after each stimulus. Participants rated higher intensity when medium stimuli were preceded by the high cue compared to the low cue ($p < 0.001$). These effects did not differ among the groups. During anticipation, we observed cue-related activation (High cue > Low cue) in the OFC across all groups. Cue effects on intensity ratings on medium trials were mediated by the anterior insula across all groups. However, when we examined whether OFC anticipatory activation moderated responses to cues during medium trials, we observed different networks of activation across modalities, consistent with domain-specific effects. Furthermore, when we compared high and low intensity stimuli within each group, we found differences in neural patterns. Specifically, the NPS and SIIPS showed larger differences for the heat group compared to the salt and sugar groups, while the affect pattern did not differ between the heat and salt groups. In conclusion, our findings suggest that predictive cues engage both domain-general mechanisms (such as the OFC and insula) and domain-specific processes in the context of heat compared to aversive and pleasant tastes.

Disclosures: **Y. Zhao:** None. **I. Lee:** None. **Q. Yu:** None. **M. Rose-McCandlish:** None. **D. Mischkowski:** None. **J. Avery:** None. **J. Ingeholm:** None. **L. Atlas:** None.

Poster

PSTR271. Human Pain Imaging

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.19

Topic: D.02. Somatosensation – Pain

Support: STI-2030 Major Project (2022ZD0206400)
National Natural Science Foundation of China (32171078)
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The Scientific Foundation of the Institute of Psychology, Chinese Academy of Sciences (E2CX4015)
Young Elite Scientist Sponsorship Program by the China Association for Science and Technology (E1KX0210)

Title: Morphological and transcriptomic decoding of accelerated brain aging in chronic pain

Authors: L. ZHAO, W. ZHAO, ***Y. TU**;
Inst. of Psychology Chinese Acad. of Sci., Beijing, China

Abstract: Patients with chronic pain (CP) are at a higher risk of dementia, but the mechanism remains unclear. Dementia-risk-related biological impairments in the brain accumulate with age but vary in velocity across different conditions, suggesting the implication to decode the neurobiological mechanisms between CP and dementia via characterizing brain aging. Considering CP is a unifying symptom in a series of highly heterogeneous conditions, whether common CP types present a general or distinct brain aging patterns that are associated with patients' cognitive functions, dementia risks, and genetic predisposition, are still unknown.
To decode accelerated brain aging in CP, we developed an MRI-based brain age model in healthy adults (N = 6,725) and applied it to examine the brain aging acceleration (quantified by the predicted age difference [PAD]) in five common types of CP (Dataset 1; N = 2734) including knee pain, back pain, headache, neck pain, and hip pain. The findings of brain aging acceleration were further validated in an independent dataset (Dataset 2; N = 192) that had baseline and 5-year follow-up sessions. The associations between brain aging acceleration and pain symptoms, cognitive function, and dementia risks were assessed cross-sectionally and longitudinally. We also employed genetically pleiotropic, imaging-transcriptomic and enrichment analyses to identify the molecular genetic basis of brain aging acceleration in CP.
Compared to healthy controls, a significantly increased PAD was only observed in chronic knee pain cohort (Cohen's d = 0.130). In the subgroups of chronic knee pain, a significant increase in PAD was found in the knee osteoarthritis (KOA) cohort (d = 0.437) but not in the subgroup without KOA. The increased PAD in KOA was replicated in Dataset 2 (d = 0.454) and was

associated with memory decline (r = 0.348) and dementia risk (Spearman's rho = 0.278). The gene SLC39A8 showed pleiotropy between brain aging acceleration and KOA, as well as transcriptional associations with KOA neuroimaging phenotypes across both datasets. The genes exhibiting transcriptional associations with KOA neuroimaging phenotypes were highly expressed in microglial cells and astrocytes, and primarily enriched in synaptic structure and neurodevelopment.
In summary, our study demonstrates the heterogeneity of brain aging in CP and unfolded a distinct heritable pattern that links KOA to dementia by providing an integrative biological profile that connects specific genes, molecular processes, and cell classes with morphological brain aging.

Disclosures: **L. Zhao:** None. **W. Zhao:** None. **Y. Tu:** None.

Poster

PSTR271. Human Pain Imaging

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.20/Z28

Topic: D.02. Somatosensation – Pain

Title: Cortical oscillations of the sensory-discriminative and affective-motivational dimensions of pain using the electroencephalogram

Authors: I. CASMEDES, N. CIVITELLO, S. LOVE, ***A. HARRIS BOZER**;
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Abstract: Pain is a complex, multidimensional phenomenon and consists of three dimensions: sensory-discriminative, affective-motivational, and cognitive-evaluative. Pain questionnaires such as the widely used McGill Pain Questionnaire contain sections that assess both the sensory and affective dimensions of pain. It is well documented that the pain dimensions are associated with activity in select cortical areas (e.g. primary somatosensory cortex for the sensory dimension and anterior cingulate cortex for the affective dimension), yet the EEG profile of the cortical activity that underlies the pain dimensions is not comprehensively known. Right-handed participants (18-30 years old) were placed into two groups: chronic pain reported (n=3) vs. no chronic pain (n=6). After an impedance check, cortical activity was recorded using an ABM B-Alert 24 electrode EEG and iMotions software (referenced to mastoids) in a double-walled and foam insulated sound attenuating chamber (Whisper Room) during presentation of previously validated sensory-discriminative and affective dimension questions from the McGill Pain Questionnaire. Frequency band data were extracted in Cartool software (fast fourier transform) after Matlab was used to filter (.05-50Hz) data and reject artifacts. ANOVAs were run to compare EEG oscillations within the frequency bands (delta .05-3 Hz; theta 4-7 Hz; alpha 8-13 Hz; beta 14-30 Hz; and gamma 31-50 Hz) by group (chronic pain vs. no pain) and dimension (sensory vs. affective dimension questions). There were no significant differences by dimension or pain group, $p>.05$. These preliminary data were collected to expand the literature by

investigating the cortical (EEG) response during the sensory- discriminative and affective dimensions using questions from the McGill Pain Questionnaire.

Disclosures: I. Casmedes: None. **N. Civitello:** None. **S. Love:** None. **A. Harris Bozer:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.01/AA1

Topic: D.03. Somatosensation – Touch

Support: NIH grant F31NS124097

Title: Distinct ascending light touch pathways differentially encode vibratory stimuli

Authors: *E. HUEY, J. TURECEK, M. M. DELISLE, M. DUA, D. D. GINTY;
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Abstract: A physiologically diverse group of mechanosensory neurons that innervate the skin underlies our abilityto perceive a remarkable range of tactile stimuli and provide us with the capacity to manipulate objects,detect threats, and navigate our environment. Despite the fundamental importance of our sense of touch,relatively little is known about how distinct ascending pathways organize and represent touch information.The dorsal column nuclei (DCN) of the brainstem, along with the spinal cord, are early sites of tactileinformation processing. Non-overlapping populations of DCN projection neurons target the ventralposterolateral nucleus of the thalamus (VPL) and the external nucleus of the inferior colliculus (ICX). Wehypothesized that these ascending light touch pathways serve distinct functional roles: the thalamicpathway may be important for fine tactile discrimination and acuity, while the collicular pathway maycontribute to innate behaviors, such as orienting in relation to salient tactile stimuli. Previous work in thelab supports this hypothesis, demonstrating that DCN neurons projecting to ICX are able to phase lockto high frequency vibratory stimuli (>250hz) while DCN neurons projecting to VPL rarely can. In order tounderstand how this dichotomy in DCN projection neuron response properties is represented indownstream brain targets, we performed *in vivo* extracellular recordings of neurons in VPL and ICX. Wefound that the VPL and ICX inversely represent vibratory stimuli, where ICX neurons are most sensitiveto vibrational stimuli between 200-500hz and VPL neurons optimally respond to low frequency stimuli inbetween 10-200hz. We hypothesized that Pacinian afferents, which are unique in their ability to encodehigh frequency vibratory stimuli, have an outsized role in shaping ICX response properties in comparisonto other primary afferent types. ICX responses to vibration were greatly attenuated in a genetic mousemodel lacking Pacinian corpuscles, whereas VPL responses were largely normal in the same model. Ourfindings demonstrate that the ascending touch pathway to the ICX is uniquely tuned to high frequencyvibratory stimuli mediated by Pacinian afferents. Ongoing experiments are determining the functionalsignificance of this high frequency bias in the context of animal

behavior. Preliminary results reveal thatsilencing the ICX reduces avoidance of a 500hz vibratory stimulus in a preference assay, suggesting thatcertain somatosensory behaviors are selectively mediated by the ICX pathway.

Disclosures: E. Huey: None. **J. Turecek:** None. **M.M. Delisle:** None. **M. Dua:** None. **D.D. Ginty:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

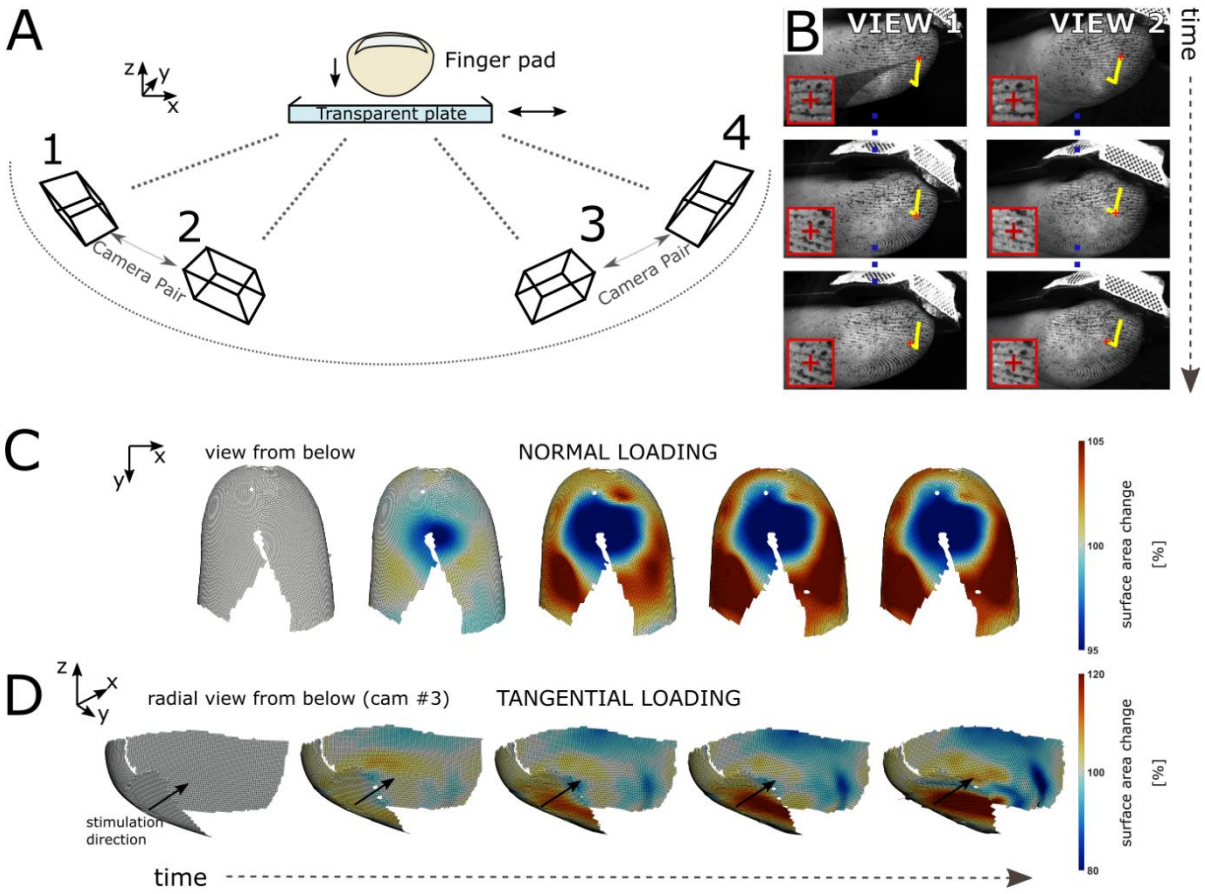
Program #/Poster #: PSTR272.02/AA2

Topic: D.03. Somatosensation – Touch

Title: 3-d reconstruction of the fingertip during tactile interactions

Authors: *D. DOUMONT[1], A. R. KAO[2], G. J. GERLING[2], A. BROWET[1], B. P. DELHAYE[1], P. LEFEVRE[1];
[1]Inst. of Neurosci. and ICTEAM, Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium; [2]Sch. of Engin. and Applied Sci., Univ. of Virginia, Charlottesville, VA

Abstract: Tactile signals underlying our perception of touch originate from the mechanotransduction of skin deformation. Quantification of such deformation during interactions between the fingertips and objects can provide new insights into the tactile information provided to the brain. Measuring skin deformation without affecting its behavior is challenging, and studies have successfully used optical imaging and digital image correlation (DIC) to reconstruct deformations at the contact interface, using a glass surface. Here, we aimed to extend those efforts and develop a method to reconstruct the 3-D deformation of the skin inside (planar) and outside (non-planar) the contact resulting from the normal and tangential loading of the fingertip over a flat surface. Using a robotic platform, the index fingertip of participants is passively pressed against a flat transparent surface (loading). Then, while maintaining the normal force constant, the surface was moved laterally at a set velocity until full slippage occurred (Fig 1A). The fingerpad is imaged by two pairs of high-resolution [2MP, 50fps] industrial cameras. A speckle pattern was drawn on the fingerpad using black ink to create a unique pattern for the DIC tracking (Fig 1B). Finally, we performed stereovision calibration and used DIC on each stereo-pair to reconstruct the skin surface in 3-D. During loading, we observed that the contact area is subjected to a radial compressive field of deformation of more than 5% at 5N, whereas the outside of the contact area expands to a similar magnitude (Fig 1C). During slip onset, deformations outside the contact are significantly larger and less homogeneous compared to the loading phase (Fig 1D). This heterogeneity could potentially be attributed to the geometry or the fingerprint of the fingertip. Those 3-D measurements will help to develop more accurate mechanical models of the fingertip and could be used concurrently with neurophysiological recordings to improve existing tactile afferent models.



Disclosures: **D. Doumont:** None. **A.R. Kao:** None. **G.J. Gerling:** None. **A. Browet:** None. **B.P. Delhaye:** None. **P. Lefevre:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.03/AA3

Topic: D.03. Somatosensation – Touch

Support: CGS-M Scholarship
Foundation Grant from the Canadian Institutes of Health Research

Title: Adaptation in low-threshold mechanoreceptors improves encoding of stimulus amplitude and frequency

Authors: A. HALAWA[1,2], L. MEDLOCK[1,2], D. AL-BASHA[1,2], C. DEDEK[1,2], S. RATTÉ[2], S. PRESCOTT[2,1];
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Abstract: Primary sensory neurons transduce and transmit all the information about the external world that the brain has access to. When presented with prolonged stimulation, sensory neurons must maintain effective information transfer despite bioenergetic constraints. We investigated spike-rate adaptation in rat hind paw low-threshold mechanoreceptors (LTMRs) recorded in vivo during 30 seconds of vibrotactile stimulation with sine waves of varying frequencies (2-300Hz) and amplitudes (150-225mN). Our goal was to explore how prolonged stimulus exposure affects not just firing rate, but also spike-timing precision. What is the basis for this adaptation, and how does it affect the mutual information between neuronal response and stimulus? Whereas spike rate quickly decreased during prolonged stimulation, spike-timing precision rapidly improved (i.e. jitter decreased), and stayed high throughout the trial. To examine how this happens, we fit neurons with general linear models (GLMs) during both early and late phases of the response. Adaptation was accounted for by changes in the refractoriness (h filter) and passive current (u) with minimal concomitant changes in the stimulus (k) filter. Stability of the stimulus filter suggests that neurons maintain the same frequency preference despite adaptation. Increased refractoriness (greater afterhyperpolarizing current) might regularize the spike train, which can decrease entrainment by increasing cycle skipping, but also improve spike-timing precision. To study the effect on coding, we calculated information gain between stimulus and neural response. We found that information per spike rapidly increases in the first second, similar to the improved precision. Despite the increase in information per spike, the decrease in spike rate late in the stimulus presentation resulted in less total information gained from the response of a single neuron. However, when we trained a discriminator to classify the stimulus parameters (frequency & amplitude) based on population-level spiking, we found that the decrease in spike rate did not limit information transfer; instead, information was lowest in the first second, after which it rapidly increased and stayed high. This followed a timeline similar to the improved information per spike, the change in linear filters, and the improved spike-timing precision. All in all, our work shows that adaptation is beneficial for coding vibrotactile input by an ensemble of LTMRs, improving the temporal coding of stimulus frequency and the rate coding of stimulus amplitude.

Disclosures: A. Halawa: None. **L. Medlock:** None. **D. Al-Basha:** None. **C. Dedek:** None. **S. Ratté:** None. **S. Prescott:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.04/AA4

Topic: D.03. Somatosensation – Touch

Title: Impact of moisture on the biomechanical response of finger pad skin

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Abstract: The human fingerpad skin contains sweat glands and sweat pores that actively regulate fingerpad moisture content. It has been observed that moisture content can have a strong impact on friction and gripping behavior during active manipulation of objects with the fingertips. It has also been hypothesized that sweat softens the skin tissues, thereby influencing fingerpad-object contact. If the mechanical stiffness of the skin is impacted by moisture content, similar mechanical constraints should lead to different deformations at different levels of moisture. Given that the tactile mechanoreceptors encode skin deformations, fingertip moisture might therefore tune the neural response of those receptors.
To test this idea, we developed and calibrated a transparent moisture sensor to make possible a continuous measure of fingertip moisture while measuring at the same time the skin mechanical deformation resulting from the loading and sliding of a transparent surface, using optical imaging. In an experiment involving 16 subjects, the index finger pad was passively contacted with a flat transparent surface at 1,2 or 5N normal force. The surface was then moved laterally at a constant speed (5mm/s) in the ulnar direction until a full slip, thereby generating substantial surface deformation in the skin. The fingertip skin moisture content was varied naturally, by using the occlusion phenomenon, or artificially by adding water or drying the skin using ether. In the occluded condition, a 30-second break was observed between the contact and the onset of slip to allow for the natural increase of moisture at the contact interface. We observed the moisture level at the contact interface, varied naturally or artificially, had a significant impact on several biomechanical parameters.
We confirmed that friction was directly impacted by moisture and reproduced previous results showing that an intermediate level of moisture maximizes friction. Moreover, while the gross contact area was mostly unaffected, real contact strongly increased with the moisture content. Finally, preliminary analyses on one subject show a significant impact of moisture on fingertip skin deformation.

Disclosures: B. Delhaye: None. **S. Lallemand:** None. **D. Doumont:** None. **P. Lefevre:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.05/AA5

Topic: D.03. Somatosensation – Touch

Support: CIHR

Title: Innervation of Meissner corpuscles in the glabrous skin of the marmoset hand

Authors: *V. SUKUMAR[1], M. FEYERABEND[2], S. EVERLING[3], J. MARTINEZ-TRUJILLO[4], W. INOUE[2], A. PRUSZYNSKI[2];
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Abstract: Cutaneous mechanoreceptors are specialized structures that respond to the stresses and strains arising from skin deformation. Meissner corpuscles (MCs) are low threshold cutaneous mechanoreceptors found in the dermal papillae of the glabrous (i.e. hairless) skin. MCs are crucial for fine, discriminative touch and vibration. Recent studies have shown that the Aβ afferent neurons innervating primate MCs signal the geometric features of touched objects [Pruszynski et al., 2014; Sukumar et al., 2022; Suresh et al., 2016]. We have suggested that this functional capacity arises because of the dendritic-like branching of Aβ afferent neurons in the skin and the spatial arrangement of the many MCs they innervate. However, beyond their existence, relatively little is known about these branching patterns in primates. Here we provide a comprehensive account of the anatomy of MCs in the glabrous skin of the marmoset hand and the neurons innervating them, including the first detailed characterization of the branching patterns. We used immunofluorescence confocal microscopy to image the marmoset glabrous skin (n=8; 4 adult male/female, 2-5 years old), including the fingertips, the intermediate phalanges, the first interphalangeal joint, and the palmar surface of the hand. We visualized MCs and their myelinated innervation, especially Aβ fibers, as well as their non-myelinated innervation. We also visualized peptidergic and non-peptidergic neurons innervating MCs. We report the following preliminary findings. MCs are located throughout the marmoset hand, at a depth of ~140μm from the surface of the skin. MCs are approximately 21μm in diameter and 35μm in length. MC density appears similar across fingertips but varies along the distal-proximal axis of the hand, with highest density in the fingertips. Each MC is innervated by at least one myelinated Aβ afferent fiber (~4μm diameter), which wraps around the lamellae in the MC. Many of the MCs in the fingertips are innervated by multiple branches of the Aβ afferent fibers, some of which arise from distinct neurons. MCs also receive non-Aβ innervations (~1μm diameter). Finally, similar to macaques and humans, Aβ neurons branch extensively, each innervating many MCs both within and across dermal ridges. Preliminary neuronal tracing indicates that, at least in the fingertip, MCs innervated by different Aβ neurons interdigitate with each other. Taken with the finding that MCs receive multiple distinct Aβ innervations, this suggests that the receptive fields of these neurons overlap substantially.

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Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.06/AA6

Topic: D.03. Somatosensation – Touch

Support: CONACyT Grant KSC514945

Title: Electrophysiological analysis of the peripheral sensory pathway related to clitoral sheath mechanoreceptors of the rat

Authors: *M. SERRANO[1], O. LARA-GARCÍA[3], M. OLOARTE FLORES[3], B. MOLINA[4], M. LARA GARCIA[2], P. PACHECO[5];
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Abstract: Clitoral sheath mechanical stimulation such as pressure, reflexively activates pubococcygeus muscle (Pcm) motoneurons which response differs according to gonadal hormone *milieu*. In diestrus phase, Pcm reflex activity evoked by clitoral pressure was only noticed during stimulation period, while in proestrous phase, this electromyographical activity was not only present during stimulation, but displayed a long-lasting post-stimulation activity namely afterdischarges. Moreover, in ovariectomized rats these afterdischarges were absent, but if a subcutaneous injection of estradiol is applied; then, these afterdischarges became restituted. Estradiol receptors (ER´s) are present not only in efferent pathways but in afferent as well, from which it is known that sensory neurons from most dorsal root ganglia posses ER´s. Thus, it is likely that these afterdischarges activity may merely be reflecting a sensory neuron hypersensitivity induced by a high estradiol milieu. Here, we explored a sensory pathway that carries peripheral information evoked by mechanoreceptors within clitoral sheath. Pre and post L_6 dorsal root ganglion electrophysiological recordings were taken from adult female Wistar rats, in diestrus and proestrous phase, ovariectomized and ovariectomized plus a single subcutaneous injection of estradiol benzoate. Pre and post ganglionic repetitive activity was present during and after mechanical stimulation in all studied groups. Post-stimulation activity duration was proportional to stimulus duration. Interestingly enough was that clitoral receptors together with its corresponding sensory axon produced afterdischarges which persist during its pass through the dorsal roots.

Disclosures: M. Serrano: None. **O. Lara-García:** None. **M. Oloarte Flores:** None. **B. Molina:** None. **M. Lara Garcia:** None. **P. Pacheco:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.07/AA7

Topic: D.03. Somatosensation – Touch

Support: CONAHCyT Grant MO1084723

Title: Glans penis sensory receptors activity by rubbing is sensitive to gonadal hormones in the rat

Authors: *M. OLOARTE FLORES[1], B. MOLINA[2], O. LARA-GARCÍA[1], Y. CRUZ[3], K. YAMADA[4], M. LARA GARCIA[5], P. PACHECO[6];
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Abstract: Sensory stimulation induces spinal reflex activity, which may last even after stimulus cessation. This post-stimulation activity may be due to bistability in spinal motoneurons. Nociceptors and thermoreceptors are sensitive to estradiol. Ganglionic cells possess estradiol receptors and respond to testosterone, at least in *in vitro* preparations. Neither sex difference nor differences in gonadal hormones effects are usually considered in *in vivo* preparations focused on sensory receptors physiology or their afferent pathways. It is known that penis afferent input is through pudendal nerve, which originates from L_6 and S_1 spinal nerves; and that testosterone is necessary to maintain histological and physiological characteristics of the penis. We have described that glans penis sensory receptors activity rely on the type of mechanical stimulation applied, from which rubbing was the only stimulus that never induced dorsal root post-stimulation activity from L_1 to S_1. Nonetheless, there is no information regarding gonadal hormone sensitivity of afferent activity originated from sensory receptors within the glans penis; then, in the present study, we recorded glans penis electrophysiological activity evoked by rubbing stimulation in L_6 and S_1 dorsal roots of adult Wistar rats gonadally intact, gonadectomized (Gdx) and Gdx with a single subcutaneous injection of testosterone propionate or estradiol benzoate. In intact animals, only phasic and tonic “on” responses were noticed. In Gdx animals, besides phasic and tonic “on” responses, there were long-lasting tonic “off” responses (afterdischarges). In Gdx rats with acute testosterone administration, only phasic and tonic “on” responses were recorded, no afterdischarges were noticed in either dorsal root following testosterone administration. Gdx rats with acute estradiol administration, did not modify afterdischarge activity. Results suggest that testosterone nor estradiol, is actively regulating sensory information arising from glans penis rubbing-related sensory receptors. This is supported by the hypersensitivity noticed in Gdx rats whose sensory receptors and/or ganglionic cells related to rubbing stimulation returned to intact-like characteristics following testosterone administration but estradiol. Thus, sensory activity in L_6 and S_1 dorsal roots ganglions possess a repetitive-like behavior that is modulated by testosterone in male rat.

Disclosures: M. Oloarte Flores: None. **B. Molina:** None. **O. Lara-García:** None. **Y. Cruz:** None. **K. Yamada:** None. **M. Lara Garcia:** None. **P. Pacheco:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.08/AA8

Topic: D.03. Somatosensation – Touch

Support: NIH grant NS097344
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The Bertarelli Foundation
The Hock E. Tan and Lisa Yang Center for Autism Research
The Lefler Center for Neurodegenerative Disorders
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Stuart H.Q. and Victoria Quan fellowship

Title: Krause corpuscles of the genitalia are vibrotactile sensors required for normal sexual behavior

Authors: *L. QI, M. ISKOLS, A. HANDLER, D. GINTY;
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Abstract: Krause corpuscles, first discovered in the 1850s, are enigmatic sensory structures with unknown physiological properties and functions found within the genitalia and other mucocutaneous tissues. Here, we identified two distinct somatosensory neuron subtypes that innervate Krause corpuscles of the mouse penis and clitoris and project to a unique sensory terminal region of the spinal cord. Using *in vivo* electrophysiology and calcium imaging, we found that both Krause corpuscle afferent types are A-fiber rapid-adapting low-threshold mechanoreceptors, optimally tuned to dynamic, light touch and mechanical vibrations (40-80 Hz) applied to the clitoris or penis. Optogenetic activation of male Krause corpuscle afferent terminals evoked penile erection, while genetic ablation of Krause corpuscles impaired intromission and ejaculation of males and reduced sexual receptivity of females. Thus, Krause corpuscles, which are particularly dense in the clitoris, are vibrotactile sensors crucial for normal sexual behavior.

Disclosures: L. Qi: None. **M. Iskols:** None. **A. Handler:** None. **D. Ginty:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.09/AA9

Topic: D.03. Somatosensation – Touch

Title: A decoding method of an inter-spike-interval (ISI) pattern based on an exponentially attenuated spike firing rate with random deviation distribution for slow adapting mechanoreceptors to pressure stimuli

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Abstract: To develop realistic metaverse systems such as virtual reality (VR), augmented reality (AR), and mixed reality (MR), it is important to implement virtual tactile technology on wearable devices such as lightweight and thin gloves and thimbles. This is because a large and heavy mechanical device is needed to generate a natural pressure stimulation. Therefore, techniques for encoding inter-spike-interval (ISI) patterns that allow tactile nerves to feel virtual pressure using electrical or micrometer-scale vibrational stimuli is necessary core technology. We first performed a study to apply pressure stimulation to the skin of mice in Ex-Vivo state and measured the spike firing pattern of slowly adapted (SA) neurons isolated from peripheral nerve bundles to decode the neuron spike pattern corresponding to pressure stimulation. More specifically, the skin and nerves (C57bl/6, 8-10 weeks) of mice were extracted, and spike signals generated by slow-adapting (SA) neurons isolated from afferent nerves were recorded by Au electrodes in paraffin oil chambers electrochemically separated from the synthetic interstitial fluid chamber, at a pH of 7.4 and temperatures 29-30℃. A neural spike response was obtained by applying a force of 10 to 100 mN for 6 seconds using a stimulus rod. When pressure stimulation is applied, the spike fires rapidly, and the firing rate decreases within 0.1 to 0.2 seconds and then randomly distributed within a certain range. And the initial firing rate is proportional to the strength of the pressure. To fit the exponentially decreasing firing rate curve, we performed the least square regression analysis using the exponentially attenuated curve. In this work, we propose an decoding method that uses random functions to add random deviations within a certain value to the exponential attenuation curve when generating neural spike patterns. By introducing random deviation components, the similarity between the experimental and simulated ISI patterns linked to the firing rate curve is greatly improved, and a quantitative evaluation index based on correlation coefficient of time and frequency dimensions about the similarity of ISI patterns is newly proposed and studied. When the random function was introduced, the correlation coefficients between the experimental and simulated ISI patterns were improved by more than 50%. Applying electrical stimulation or micrometer-scale vibration stimulation to finger with the encoded signals obtained based on the reverse direction of the decoding model derived using this newly proposed method can provides a more natural pressure sensation to human.

Disclosures: **K. Park:** None. **Y. Kang:** None. **Y. Choi:** None. **H. Cho:** None. **S. Jung:** None. **S. Lee:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

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Program #/Poster #: PSTR272.10/AA10

Topic: D.03. Somatosensation – Touch

Support: NIH grant NS097344
Gordon Postdoctoral Fellowship
Mahoney Postdoctoral Fellowship
Tan-Yang center for Autism Research

Title: The mechanosensation of active movement

Authors: *J. TURECEK, D. D. GINTY;
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Abstract: Pacinian corpuscles are exquisitely sensitive to high-frequency mechanical vibrations from 50-1000 Hz. However, it is unclear how vibration is encountered and detected during unconstrained behavior. Here, we record from Pacinian corpuscles in awake, freely moving mice. In awake animals, Pacinians can reliably encode subtle surface vibrations, and when standing on certain substrates, can easily detect mechanical activity from over a meter away. During movement, the firing rate of most Pacinians is higher than any other low-threshold mechanoreceptor or proprioceptor. The firing of Pacinians can encode information about the type of material making contact with the limb, as well as the nature of self-contact. In addition to surface vibrations and locomotion, we find that Pacinians are also robustly activated during a wide variety of natural behavior, including grooming, digging, climbing and interactions with other animals. Pacinians in the hindlimb are sensitive enough to be activated by forelimb- or upper-body-dominant behaviors. Finally, we find that their responsiveness during awake behavior is strongly dependent on their sensitivity and frequency tuning. Thus, natural behavior generates a wealth of mechanical vibrations that can be encoded by Pacinian corpuscles, detecting both self-generated movement and externally generated vibrations within the environment. The diverse tuning of Pacinians enables rich sensory coding across a wide variety of behaviors, even those that are not typically associated with vibration.

Disclosures: J. Turecek: None. **D.D. Ginty:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.11/AA11

Topic: D.03. Somatosensation – Touch

Support: Link Foundation Modeling, Simulation, and Training Fellowship
Leverhulme Trust Grant RPG-2022-031
NSF Award 1751348

Title: Biomechanical filtering diversifies tactile encoding in whole-hand Pacinian corpuscle neuron populations

Authors: *N. TUMMALA[1], G. REARDON[2], B. DANDU[1], Y. SHAO[5], H. P. SAAL[6], Y. VISELL[3,4,1,2];
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Abstract: The human hand contains hundreds or more exquisitely sensitive Pacinian corpuscle neurons (PCs) that encode vibrotactile information during manual touch interactions. When directly stimulated, PCs exhibit highly similar response characteristics, with the highest sensitivity to frequency components near 250 Hz. Given that touch-elicited skin oscillations travel readily across the whole hand and excite large numbers of widespread PCs, the relative homogeneity of PC response characteristics suggests a degree of redundancy that is difficult to reconcile with principles of efficient neural encoding. Here, we show that biomechanical filtering reduces redundancy and promotes heterogeneity in PC population responses by modifying signal transmission across the hand. We characterized the biomechanical transmission of touch-elicited skin oscillations by collecting spatiotemporally resolved optical vibrometry measurements across the glabrous skin of human hands (N=7) for each of four stimulus contact locations. The vibrometry data revealed hand biomechanics to impart complex frequency-dependent patterns of attenuation due to the soft tissue mechanics and morphology of the hand. To investigate the implications of these findings for tactile encoding in the PC system, we used the collected vibrometry measurements to drive whole-hand populations of simulated PC neurons. We found that biomechanical filtering diversified response characteristics across PC populations by modifying the frequency content in skin oscillations transmitted to PC locations prior to mechanotransduction. As a result, correlations between the response characteristics of PCs near the contact location and those of PCs outside the contact region decreased with increasing distance. Moreover, PCs across the hand exhibited a range of peak sensitivities (25-500 Hz) significantly wider than is observed when PCs are directly stimulated (200-300 Hz). Biomechanical filtering also reduced redundancy in PC firing rates and spike timing, as determined through principal component analysis and interspike interval information entropy. Our findings show how biomechanical filtering serves as a pre-neuronal mechanism for diversifying PC population responses, thereby supporting encoding efficiency in the PC channel. Our vibrometry-driven computational model of PC population responses also supplies a valuable tool for investigating the neuromechanical basis of tactile encoding in the periphery.

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Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.12/AA12

Topic: D.03. Somatosensation – Touch

Support: NIH intramural funding

Title: Piezo2 and perineal mechanosensation are essential for sexual function

Authors: *R. LAM[1], L. J. VON BUCHHOLTZ[2], M. FALGAIROLLE[3], J. OSBORNE[3], E. FRANGOS[4], R. SERVIN[6], M. NAGEL[2], M. NGUYEN[3], M. JAYABALAN[5], D. SAADE[7], A.

PATAPOUTIAN[8], C. BÖNNEMANN[2], N. RYBA[2], A. T. CHESLER[9];
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Abstract: Despite the potential importance of genital mechanosensation for sexual reproduction little is known about how perineal touch influences mating. Here we explored how mechanosensation affords exquisite awareness of the genitals and controls reproduction in mice and humans. Using genetic strategies and in vivo functional imaging, we demonstrated that the mechanosensitive ion channel Piezo2 is necessary for behavioral sensitivity to perineal touch. Notably Piezo2-function is needed for triggering a touch evoked erection reflex and successful mating in both male and 25 female mice. Humans with complete loss of PIEZO2 function have genital hyposensitivity and experience no direct pleasure from gentle touch or vibration. Together, our results explain how perineal mechanoreceptors detect the gentlest of stimuli, trigger physiologically important sexual responses, providing a platform for exploring the sensory basis of sexual pleasure and its relationship to affective touch.

Disclosures: R. Lam: None. **L. J. von Buchholtz:** None. **M. Falgairolle:** None. **J. Osborne:** None. **E. Frangos:** None. **R. Servin:** None. **M. Nagel:** None. **M. Nguyen:** None. **M. Jayabalan:** None. **D. saade:** None. **A. Patapoutian:** None. **C. Bönnemann:** None. **N. Ryba:** None. **A.T. Chesler:** None.

Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

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Topic: D.03. Somatosensation – Touch

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HBI Young Scientist Transitions Award
American Diabetes Association Postdoctoral Fellowship
Simons Collaboration on the Global Brain Transition to Independence Postdoctoral Award
Howard Hughes Medical Institute

Title: Interoceptive receptive fields and functional architecture of physiological control in the mouse brainstem

Authors: *C. RAN[1], J. BOETTCHER[1], J. A. KAYE[1], C. E. GALLORI[1], S. D. LIBERLES[2];
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Abstract: Our external senses of sight, smell, sound, touch, and taste enable us to perceive the external world. In addition, our internal sensory system monitors the physiological states of peripheral organs, such as mechanical and chemical cues from ingested food, irritants in the airway that induce cough, and inflammatory cues that signal tissue damage. In comparison to external sensory systems, the principles that define visceral sensory processing remain poorly defined. Here, we developed an *in vivo* two-photon calcium imaging preparation to understand internal organ representations in the nucleus of the solitary tract (NTS), a sensory gateway in the brainstem that receives vagus and other inputs from the body. Combining the imaging platform with stimulation of visceral organs, we uncover diverse neuronal responses to internal stimuli, while functionally defined cell types are highly organized within the NTS. Combining functional imaging with pharmacogenetic manipulations and viral tracing from genetically defined vagal sensory cell types, we show that the highly organized representations of internal senses are generated by vagal axon sorting and higher-order sensory processing within the NTS. Ongoing work will connect the response profiles of NTS neurons to the connectivity to downstream target areas. Together, our study reveals basic coding principles used by the brain to process visceral inputs and may shed light on the treatment of viscerosensory and autonomic dysfunctions.

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Poster

PSTR272. Tactile Processing: Periphery, Spinal Cord, and Brainstem

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.14/AA14

Topic: D.03. Somatosensation – Touch

Support: NIH Grant R01NS089652
NIH Grant 1R01NS104834-01

Title: Trigeminal innervation and tactile responses in mouse tongue

Authors: *L. ZHANG[1,3,4], M. NAGEL[5], W. OLSON[2,3,4], A. T. CHESLER[6], D. H. O'CONNOR[2,3,4];
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Abstract: The mammalian tongue is richly innervated with somatosensory, gustatory and motor fibers. These form the basis of sophisticated sensorimotor functions such as the determination of

object shape and texture during active touch. Despite high tactile acuity and sensitivity revealed by human behavioral and microneurography studies, the neural basis of tongue mechanosensation remains largely mysterious. In particular, the relationship between electrophysiological responses and anatomical innervation patterns of distinct sensory neuron types remains unclear. Here we found that sensory neurons in the trigeminal ganglion (TG) innervated both fungiform papillae and filiform papillae of the tongue, unlike gustatory afferents from the geniculate ganglion which innervate only the fungiform papillae that contain taste buds. Trigeminal afferents were the main source of Piezo2+ afferents in the fungiform papillae, which terminated at the extragemmal region and exhibited a ring-like terminal pattern surrounding the taste pore. Myelinated lingual afferents in the mouse fungiform and filiform papillae did not form corpuscular sensory end organs but rather had only free nerve endings. In contrast, in the ferret tongue we found sensory end organs in filiform papillae with shapes that resembled Krause end bulbs. Single-unit recordings from TG in anesthetized mice revealed two types of lingual low-threshold mechanoreceptors (LTMRs) with conduction velocities in the Aδ range or above and distinct response properties: intermediately adapting (IA) units and rapidly adapting (RA) units. IA units were sensitive to static indentation and stroking, while RA units had a preference for tangential forces applied by stroking. Lingual LTMRs were not directly responsive to rapid cooling or chemicals that can induce astringent or numbing sensations. Genetic labeling of lingual afferents in the tongue revealed at least two types of nerve terminal patterns, involving dense innervation of individual fungiform papillae by multiple putatively distinct afferents, and relatively sparse innervation of filiform papillae. Together, our results suggest a simple model that links the functional and anatomical properties of tactile sensory neurons in the tongue.

Disclosures: L. Zhang: None. **M. Nagel:** None. **W. Olson:** None. **A.T. Chesler:** None. **D.H. O'Connor:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.01/AA15

Topic: D.05. Auditory & Vestibular Systems

Support: University of Oklahoma internal funds

Title: Default mode network function, neural oscillatory modulation, and autistic characteristics in individuals with misophonia

Authors: *M. M. MORGAN[1], J. E. NORRIS[2], L. E. ETHRIDGE[2];
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Abstract: Misophonia is characterized by intense emotional and physiological reactions to specific auditory stimuli. People with misophonia exhibit differences in brain activity in the auditory cortex and salience networks during auditory tasks. Because individuals with autism

spectrum disorder (ASD) often experience similar sensory hypersensitivities, similarities in brain activity between the two groups may suggest shared neurobiological pathways. To better understand the neural underpinnings of misophonia and its potential relationship with ASD, this study examines potential deviations in neural oscillations related to the default mode network that may contribute to the overall phenotype of individuals with misophonia. Participants (16 individuals with misophonia and 17 non-misophonic controls) ages 18-22 (M = 18.91, SD = 1.01, 88% female) completed the Broad Autism Phenotype Questionnaire (BAPQ) and an eyes open/eyes closed resting electroencephalography (EEG) task. Compared to controls, individuals with misophonia exhibited increased BAPQ rigidity scores and trended towards increased aloofness and pragmatic language scores, (Rigid: $t(31) = -2.34$, $p = .026$, $d = -.81$; Aloof: $t(31) = -1.71$, $p = .097$, $d = -.59$; Pragmatic Language: $t(31) = -1.92$, $p = .064$, $d = -.67$). Individuals with misophonia trended towards decreased alpha reactivity (ratio of eyes open to eyes closed) relative to controls $t(29) = 1.75$, $p = .091$, $d = .63$. Correlations across both groups were found between increased eye closed occipital peak alpha frequency (PAF) and increases in both BAPQ pragmatic language ($r = .355$, $p = .042$) and rigidity ($r = .387$, $p = .026$) scores. When limiting correlations to misophonia only, correlations emerged between both frontal and occipital PAF during the eyes closed condition and the BAPQ rigidity subscale score (frontal PAF: $r = .496$, $p = .043$, occipital PAF: $r = .487$, $p = .048$) but not pragmatic language scores. Individuals with misophonia exhibited decreased occipital theta-gamma phase-amplitude coupling (PAC) compared to controls, $t(28) = 2.57$, $p = .016$, $d = -.39$, and also trended toward decreased frontal theta-gamma PAC compared to controls, $t(31) = 1.92$, $p = .064$, $d = -.53$. However, individuals with misophonia did not significantly differ from controls on alpha-gamma PAC. Theta-gamma PAC has been related to network switching during shifts in cognitive load, while alpha reactivity is associated with modulation of the default mode network; these results may provide some preliminary support for the notion that misophonia involves deviations in default brain state functioning and that these differences may be related to subthreshold ASD-like characteristics.

Disclosures: **M.M. Morgan:** None. **J.E. Norris:** None. **L.E. Ethridge:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.02/AA16

Topic: D.05. Auditory & Vestibular Systems

Support: NIH DC019090
Whitehall Foundation
Magnificent Michigan Research Fellowship

Title: Population coding of time-varying sounds in the non-lemniscal Inferior Colliculus

Authors: K. SHI[1], G. QUASS[1], M. M. ROGALLA[1], A. FORD[1], J. E. CZARNY[1], *P. APOSTOLIDES[2];
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Abstract: The inferior colliculus (IC) is an evolutionarily conserved midbrain structure playing pivotal role in processing amplitude modulation (AM) of sound envelope, a key feature in conspecific vocalizations and human speech. The IC is comprised of several sub-regions: A primary central region receives ascending auditory inputs from the brainstem and projects to primary auditory thalamus, while non-primary "shell" regions integrate intra-collicular inputs and project to behaviorally relevant, higher-order thalamic regions interfacing with the amygdala, striatum and non-primary auditory cortex. While decades of studies on AM coding have focused on central IC neurons, whether and how AM sounds are encoded in shell IC neurons are underexplored, owing to the challenges of recording from these neurons located near the tectal surface. Here, we used 2-photon calcium imaging to study how shell IC neurons of awake, head-fixed mice respond to sinusoidal amplitude modulated (sAM) narrow-band noise (65-70 dB SPL, 5-200 Hz modulation rate, 0-100% modulation depth, carrier bandwidth: 16 ± 2 kHz). The calcium indicator GCaMP6f/6s/8s was expressed in shell IC neurons of 5-8 weeks old mice; 2-photon microscopy was used to record neural activity in the shell IC as the mice were passively listening to sAM stimuli of varying modulation depths and rates. We analyzed responses from 1213 sound-responsive neurons recorded from 13 mice. We find that all the major sAM tuning properties previously described in the central IC — low-pass, high-pass, band-pass, and band-reject — are similarly identified in both excitatory and inhibitory shell IC neurons. Overwhelmingly, increasing modulation depth of sAM sound enhanced shell IC neuron responses to preferred and non-preferred modulation rates, indicating a monotonic encoding of modulation depth and limited mixed selectivity to specific combinations of modulation rate and depth. Although most individual shell IC neurons display low neurometric discriminability and selectivity for sAM signals we find that sAM information is accurately represented in the shell IC based on a neural population code. Specifically, modulation rate is well-represented in the shell IC and such representation is heavily dependent on the modulation depth. Altogether our data uncovers a substantial population level AM representation in the non-lemniscal regions of the IC, thus shedding light on the building blocks of complex sound perception.

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Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

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Title: Phase coding in phoneme processing slows with age

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Abstract: Age-related hearing loss is a growing problem in aging societies. Listening difficulties occur even if audiometric thresholds indicate normal hearing, a feature possibly linked to cochlear synaptopathy. We tested passive electrical brain responses to syllables (/du/, /bu/, /di/, /bi/, /o/, and /y/), while 80 participants (55f, 25m) watched a silent movie. Measuring phase and amplitude of the most prominent entrained EEG response at 116 Hz based on continuous wavelet transformation revealed a relation to age-dependent hearing loss. EEG amplitude and phase were correlated with PTA4, PTA-EHF (10-16 kHz), broadband OLSA (with and without noise) and age. Specifically, an increase in speech processing delay was linked to a speech comprehension deficit (OLSA) as well as with hearing loss in extended high-frequencies. As the absolute temporal delays were in the order of 1-2ms, which is beyond expected values for brainstem delays, we reason that thalamic and cortical processing is mainly responsible for this age-related slowing. We conclude that a decrease in temporal coding is related to a decrease in phoneme discrimination and hearing threshold in particular at high frequencies.

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Poster

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Title: Inferior colliculus neurons are sensitive to sub-millisecond variations in sound onset duration

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Abstract: Rapid acoustic onsets are prominent in natural sounds, including in speech, such as after gaps, and in adventitious sounds, such as rustling noises. Octopus cells (OCs) in the cochlear nucleus are highly responsive to these rapid onsets and drive precisely timed inhibition in the inferior colliculus (IC) via the ventral nucleus of the lateral lemniscus[1]. However, the function of OC-driven onset inhibition in the IC remains unknown. There are several divergent models for the role of this onset inhibition in the circuit function of the IC, including: suppressing spectral splatter; preserving excitatory/inhibitory balance during onsets; and facilitating feature binding. [2,3]. To begin to arbitrate between these models, we examined the impact of onset gate duration on computational models and Neuropixel recordings of neural responses to single tones in IC of mice. We have characterized the theoretical limit, and simulated cochlear extent, of spectral splatter in natural sounds, and tones with varying onset gate durations, and find that changes in spectral splatter due to sub-millisecond differences in onset gate duration are recapitulated by the cochlea. During presentation of single tones with manipulated onset gate durations, we record neural response properties in the IC of head-fixed, awake mice. We find that sub-millisecond gate duration affects tone-evoked firing by up to 2-fold (N=3) particularly at tone carrier frequencies away from best frequencies, indicating that population responses in IC are strongly impacted by spectral splatter. Future optogenetic work will test the potential role of OCs in spectral splatter suppression. Ongoing analyses are determining the implications of our results for models of the function of rapid onset inhibition in IC.
[1] Oertel, D., Cao, X. J., Ison, J. R., & Allen, P. D. (2017). Cellular computations underlying detection of gaps in sounds and lateralizing sound sources. *Trends in neurosciences*, *40*(10), 613-624.
[2] Spencer, M. J., Nayagam, D. A., Clarey, J. C., Paolini, A. G., Meffin, H., Burkitt, A. N., & Grayden, D. B. (2015). Broadband onset inhibition can suppress spectral splatter in the auditory brainstem. *PloS one*, *10*(5), e0126500.
[3] McGinley, M. J. (2014). Rapid Integration Across Tonotopy by Individual Auditory Brainstem Octopus Cells. In *The Computing Dendrite* (pp. 223-243). Springer, New York, NY.

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Poster

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Title: Age-induced modulation in sound-evoked local field potentials in the inferior colliculus of CBA/CaJ mice

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Abstract: The inferior colliculus (IC) is a major midbrain convergence site critical for processing complex sounds such as speech and undergoes fundamental changes with age-related hearing loss (ARHL). The loss of peripheral inputs and senescence-related alterations in neurotransmission lead to decreased activity driving neurons in the IC, causing spectral-temporal auditory processing deficits. Local field potentials (LFPs) represent the electrical potential surrounding neurons in the extracellular space, reflecting pre-synaptic activity and the integration of excitatory and inhibitory signals from neuronal inputs generating action potentials. In the current study, age-related changes in sound-evoked LFPs were assessed in the CBA/CaJ mouse model of ARHL via deconstructing various LFP components evoked by wideband noise bursts. To assess the effects of age on pre-synaptic sound-evoked activity in the IC, multi-channel arrays were placed in the IC central nucleus and neural activity was acquired from 11 young (4-6 mo.), 10 middle-aged (8-14 mo.), 20 old (24-25 mo.), and 6 very old (27-30 mo.) mice. Only one session and recording location was selected per animal as not to bias further analyses by over representing data from any single animal. LFPs were recorded from linear 16-channel NeuroNexus probes sampled at 1017 Hz and down-sampled to 2-300 Hz. 589 recording sites were characterized into low, mid, or high frequency regions based off the tonotopic arrangement of the IC. LFPs were temporally decomposed into several regions, based on the amplitude and time of the component of interest.Statistically significant age effects at 80 dB SPL stimuli were found in both the magnitude and latency of temporal LFP components across all frequency regions. Old mice exhibited significantly larger N1 peaks than young in the low (130uV) and mid (98uV) frequency regions. Young mice exhibited the highest P1 peak magnitudes to mid and high frequencies with a 27uV higher P1 versus middle-aged animals at mid and 22-30uV higher P1 amplitudes than older mice at high frequencies. The magnitude of the N2 was 51.6 to 54.3uV deeper for young compared to both old and very old animals at low frequencies while only 41.8uV deeper at mid frequencies. Statistically significant changes in latency of temporal features of the LFP were also observed. The results of this study indicate a significant age-related modulation of both excitatory and inhibitory components of the LFP in aged auditory midbrain neurons. These changes vary as a function of tonotopy and may be related to known age-related alterations in auditory midbrain neurochemistry.

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Poster

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Topic: D.05. Auditory & Vestibular Systems

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Title: Connectivity and electrophysiology in binaural and asymmetric integration of temporal information

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Abstract: Frequency is differentially perceived depending on laterality of the stimulated ear, suggesting a hemispheric lateralization of auditory processes. Few studies have examined the extent of lateralization of auditory temporal processes. For instance, behavioral studies either suggested a lateralization of temporal resolution functions in normal hearing subjects (Brown & Nicholls, 1997; Sulakhe et al., 2003) or no lateralization at all (Baker et al., 2008; Efron et al., 1985). Moreover, it is still unknown whether binaural integration of temporal information can enhance its perception as it has already been demonstrated with intensity summation. A binaural effect on temporal resolution was suggested by Baker et al. (2008) data but no conclusions could definitely be drawn from the study. Our work aims to explore electrophysiological correlates of temporal resolution asymmetry and binaural summation in normal hearing subjects using both behavioral and electrophysiological tasks. Asymmetry will be explored using the left/right lateralization but also using the observed behavioral ear advantage lateralization. 30 subjects aged 18 to 40 with verified normal hearing were recruited. All tasks were presented in 3 conditions : left, right and binaural stimulation. Stimuli used in the study were 200 ms broadband pink noises and presented through ER-2 earphones. Hearing thresholds were determined using a 3 alternative forced choice 1up-3down psychometric staircase procedure. Then, all stimuli were sent at a comfortable intensity level of 40dBSL, thus with adapted intensities for each of the left, right and binaural conditions. A gap detection task was then performed using the same psychometric staircase procedure. The electrophysiological tasks were performed using the optimal multideviant paradigm (Duda-Milloy et al., 2019; Näätänen et al., 2004) with gap deviants stimuli of 2 ms, 5 ms, 7 ms, 15 ms and 30 ms. All deviants were pseudo-randomized and had a 10% chance of being presented. The EEG was recorded using the BrainVision 64 active electrode cap with ActiChamp and Neuroscan SynAmps 2 amplifiers. The Mismatch Negativity was used as an index of electrophysiological temporal resolution thresholds. EEG data were analyzed through Brainstorm and connectivity was measured through bivariate Granger causality using the ICBM152 2023b head model. Preliminary results suggest an ear advantage as well as a binaural summation in temporal resolution processes. These results indicate a lateralization of temporal resolution in the brain, not constrained to the right or left hemisphere, as well as a binaural central integration of such an early process.

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Poster

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Title: Arousal-driven modulation of cell-type specific sensory processing in the auditory cortex

Authors: *K. J. KAUFMAN[1], R. F. KRALL[1], M. P. ARNOLD[1], R. S. WILLIAMSON[2];
[2]Otolaryngology, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The interplay between external inputs and internal states, such as arousal, shapes the neural basis of perception. Arousal states, reflected by pupil diameter, exert continuous influence on the neocortex, impacting membrane potentials, cortical state, neuronal gain, and sensory processing. We hypothesized that pupil-linked arousal states would have a diverse influence on the cortex as stimulus encoding recruits an array of distinct cell types that span the cortical lamina (i.e., intratelencephalic (IT), extratelencephalic (ET), and corticothalamic (CT) cells). To decipher the role of arousal on sensory coding, we investigated the response properties of these populations in the auditory cortex (ACtx) using two-photon calcium imaging and full-face videography in awake mice. We first inspected the response strength to pure tone stimuli of layer (L) 2/3, L5 IT, ET, and CT cells. Increases in arousal enhanced the activity in all cell populations except L5 IT cells. Reliability analysis revealed that ET and CT activity is most reliable (less variable) when pupil is large, while L2/3 and L5 IT cells exhibited consistent reliability across arousal states. To compare excitability at high and low states, we calculated a modulation index for every cell. Values of this index closer to -1 implies higher responses at low states respective to high states, whereas values closer to +1 indicates the opposite effect. L5 IT cells had the highest variability and lowest mean modulation index, whereas ET cells displayed the lowest variability and highest mean modulation index. These findings illustrate a modulation motif in ET cells whereby an increase in activity coincide with heightened alertness. To explore the effects of arousal on spontaneous and evoked activity, we employed a multivariate regression model to predict a cell's activity on a given trial based on pupil diameter and its neural response (Schwartz et al., 2020). Our analysis revealed heterogeneity in how pupil size correlates with baseline and sound-evoked activity, encompassing both suppression and enhancement effects. Notably, L5 IT cells demonstrated a more uniform distribution of pupil effects compared to other populations. We also presented broadband noise to examine shared trial-to-trial response variability and found that higher states coincided with a decrease in shared variability in these cell types. This suggests that wakefulness alters correlated neural activity uniformly, highlighting the role of arousal in shaping functional connectivity. Collectively, our findings provide key

insights into the intricate relationship between arousal and cell-type-specific activity during sensory coding.

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Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

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Topic: D.05. Auditory & Vestibular Systems

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Title: The dorsal cortex of the mouse inferior colliculus processes the Spectrotemporal features of sound through novel cellular organizations that are dynamically modulated by sound intensity.

Authors: *B. A. IBRAHIM, Y. SHINAGAWA, A. DOUGLAS, G. XIAO, A. R. ASILADOR, D. A. LLANO;
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Abstract: The inferior colliculus (IC) is an information processing hub that receives widespread convergent auditory projections. While the dorsal cortex (DC) - the non-lemniscal division of the IC- receives major auditory cortical projections, some reports showed that the DC is a tonotopic structure, which indicates the structure's ability to integrate the basic spectral features of sound to process the complex auditory information. However, it is unclear if the DC has another level of mapping to integrate the different spectral and temporal features of complex sounds across different sound levels. Therefore, the two-photon imaging of the calcium signals was used to track the neuronal response of the DC to sounds of different degrees of spectral and temporal complexity such as pure tones (PT), amplitude unmodulated (UN), and modulated (MN) broadband noise. In addition to the tonotopic map, the DC showed a periodtopic organization where the cells of a medial rostrocaudal area were best tuned to UN separating medial and lateral regions where the cells were best tuned to MN. Analyzing the neuronal response to each tested sound was used to generate spectral and temporal indices for each neuron, which were then used to map the DC based on the dynamics of the neuronal responses across different sound amplitudes. The DC showed a cellular organization that mapped the DC surface into two main regions: dorsomedial (DMC) and dorsolateral (DLC) cortices. At the lowest tested sound level (40 dB SPL), the DMC was more responsive to simple tones (i.e. PT) and less responsive to complex sounds (i.e. UN and MN) compared to the DLC. Although increasing the sound level increased the percentage of responsive cells in both DMC and DLC, it dynamically modulated the cells of the DMC to be more responsive mostly to UN without changing the response profile of the DLC. These data suggest that the DC is mapped to process the different spectrotemporal

features of sound based on the sound intensity to probably enhance the segregation of different sound sources.

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Poster

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Topic: D.05. Auditory & Vestibular Systems

Title: Neural correlates of auditory category learning of FM sweeps in the mouse auditory cortex

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Abstract: Category learning is a fundamental brain process that enables quick and accurate response to novel stimuli in complex sensory scenes. In the auditory modality, category learning underlies many processes of sound perception, such as understanding of language in humans. While the learning process has been shown to be accompanied by changes in neuronal representation, its underlying mechanisms are not yet clear. Using an automated learning platform, we trained female mice (n = 22) to discriminate between two categories: rising frequency modulated (FM) sweeps and falling FM sweeps. At the end of training, we presented mice with novel stimuli in order to decipher the learned categorization rule and found that they the used frequency content of the sweep as the categorical boundary cue, rather than the slope of the sweep. Using the multiarray silicon probe, Neuropixels, we performed electrophysiological recordings from the auditory cortex of awake mice (n = 9 experts, n = 4 naïve) while listening passively to FM sweeps and pure tones. We acquired data from primary auditory cortex (AUDp, n = 389 neurons) and the auditory temporal association cortex (TeA, n = 91 neurons) and found that more neurons of expert mice prefer the frequency of the category boundary as compared to naïve mice. Furthermore, neurons of expert mice as well their population activity have higher discriminability between sets of both FM sweeps and pure tones. Our results show that the plastic changes in neuronal discriminability of sounds by neurons in the auditory cortex correspond to the behavioural strategy used by the mice to categorize sounds.

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Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

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Topic: D.05. Auditory & Vestibular Systems

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Title: Exogenous BDNF application alters ionic currents in a spatial and temporal manner in the avian auditory brainstem

Authors: *K. MCLELLAN[1], M. TAKAHASHI[1], H. HONG[2], G. ORDIWAY[1], J. T. SANCHEZ[1];
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Abstract: Neurotrophins are growth factor proteins that mediate normal neuronal development by using spatial and temporal signaling gradients. While neurotrophins are critical for peripheral auditory development, it is unknown how they affect the functionality of central auditory structures. The chicken nucleus magnocellularis (NM), an analogous brainstem structure to the mammalian anteroventral cochlear nucleus, provides a model system where neurotrophin signaling between brain-derived neurotrophic factor (BDNF) and its high-affinity tyrosine receptor kinase B (TrkB) is temporally and spatially regulated. Not only is it unknown how auditory brainstem neurons within NM respond to BDNF-TrkB signaling, but it is unclear whether neurotrophins affect NM in a tonotopically or developmentally distinct manner. To investigate this, we exogenously applied BDNF on NM neurons *ex vivo* and studied the neurons' intrinsic properties using whole-cell patch clamp electrophysiology. BDNF application significantly reduced outward potassium currents and increased aberrant neuronal excitability for NM neurons earlier in development, when TrkB expression is relatively high. Additionally, high frequency NM neurons at this early developmental stage exhibited stronger changes to their intrinsic properties compared to low-frequency neurons. Little to no changes were seen to mature NM neurons, which express virtually no TrkB receptor at this stage in development. This demonstrates that BDNF-TrkB signaling causes neuronal alterations within the auditory brainstem that likely promote the normal development of a mature auditory system. Elucidating the effects of exogenous neurotrophins on the auditory system is not only an essential step to infer the effects of neurotrophins *in vivo*, but it has vital consequences for the use of neurotrophins as therapeutics for auditory-related disorders.

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Poster

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Title: Investigating how neurons invariantly encode pitch derived from two types of acoustic cues

Authors: *V. TARKA[1], Q. GAUCHER[2], K. WALKER[3];
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Abstract: Pitch is our perception of the tonal quality of sound. It is the basis of musical melody and plays a key role in communication and sound segmentation. The pitch is perceived at a single fundamental frequency (F0), which can be derived for a complex sound from either the regular spacing of harmonics in the frequency domain, the repetition rate of the sound's waveform in time, or a combination of these features. Studies in marmosets have described specialized neurons located within a "pitch centre" in auditory cortex that encode F0 invariantly to other spectral changes, but there has not been clear evidence for such specialized pitch neurons in other species. We performed Neuropixels recordings of single neurons in the auditory cortex of 4 anaesthetized ferrets while presenting a variety of pitch-evoking sounds across a range of F0s (0.25-4 kHz). We found that some neurons derived F0 exclusively from resolved harmonics, while others from temporal periodicity. A further subset of neurons encoded F0 invariantly across both classes of pitch cues, which may be the first evidence for specialized "pitch neurons" in non-primates. These neurons were not confined to a localized pitch centre, as in the marmoset, but were instead distributed throughout primary auditory cortex (A1 and AAF). F0 tuning in these neurons was robust across many complex sounds but usually failed to extend to the frequency of pure tones. This suggests some auditory cortical neurons may be specialized to represent the pitch of complex sounds, and these may differ from neurons that represent the frequency of pure tones.

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Poster

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Biotechnology and Biological Sciences Research Council (BB/P007201/1, J.F.L.)

Title: Contextual modulation is a stable feature of the neural code in auditory cortex of awake mice

Authors: M. AKRITAS[1], A. G. ARMSTRONG[1], J. M. LEBERT[1], A. F. MEYER[2], M. SAHANI[3], *J. F. LINDEN[1,4];
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Abstract: The perceptual salience of a sound depends on the acoustic context in which it appears. Single-neuron correlates of this contextual sensitivity can be estimated from neuronal responses to complex sounds using the nonlinear-linear "context model" (Williamson et al. 2016 Neuron). Context models provide estimates of both the principal (spectrotemporal) receptive field of a neuron and a "contextual gain field" describing its nonlinear sensitivity to combinations of sound input. Previous studies of contextual gain fields in auditory cortex of anesthetized mice revealed strong neuron-specific patterns of nonlinear sensitivity to sound combinations. However, the stability of these patterns over time, especially in awake animals, is unknown. We recorded electrophysiological activity of neurons in auditory cortex of awake mice over many days using chronically implanted tetrode arrays. Concurrently we recorded locomotor activity and pupil diameter to measure behavioural state. Repeated recordings were made at each recording site across at least five days, during presentations of prolonged complex sounds (dynamic random chord stimuli). We used spike-waveform matching to identify the same units recorded on different days, and the context model to estimate principal receptive fields and contextual gain fields for each neuron in each recording session. We then quantified the stability of these fields both within and across days. We also examined the dependence of context model fits on measures of behavioral state. Contextual gain fields of auditory cortical neurons in awake mice were remarkably stable across many days of recording. In more than 90% of the 69 neurons tracked for multiple days, neuron-specific patterns of sound combination sensitivity (and spectrotemporal sensitivity) remained stable on a timescale that matched or substantially exceeded the typical five-day range of our measurements. Interestingly, there were small but significant effects of changes in locomotion or pupil size on the ability of the context model to fit temporal fluctuations in the neuronal response. We conclude that contextual sensitivity is an integral and stable feature of the neural code in the awake auditory cortex, which may be modulated by behavioral state.

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Poster

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Title: Early acoustic experience degrades rhythm perception of rats

Authors: Y. SUN, ***Y. ZHANG**;
East China Normal Univ., Shanghai, China

Abstract: Objective The early postnatal brain exhibits a high degree of plasticity, which facilitates its rapid structural and functional development in responding to multimodal sensory inputs. However, this plasticity also makes the developing brain vulnerable to atypical sensory experiences during early postnatal stages, leading to more pronounced degradation of higher-order brain functions such as learning & memory, reading comprehension, and social interaction in adulthood. How these atypical early sensory experiences might affect the communication-related function remains largely unstudied. **Methods** Our previous work has revealed the synaptic plasticity mechanism underlying the impact of early sensory experiences on spatial learning and memory (Proc Natl Acad Sci U S A. 2021 Jan 7;118(1):e2017841117. doi: 10.1073/pnas.2017841117.). In the present study, we investigated the impact of early acoustic experience on rhythmic perception, which plays a crucial role in vocal communication and speech, by using rat as a research model. In vivo whole-cell patch-clamp was used to investigate millisecond level changes in post-synaptic currents in auditory cortex neurons during rhythm perception. **Results** Early acoustic stimulation interfered with the development of inhibitory interneurons in the microcircuit of the rat auditory cortex, which in turn disrupted the temporal balance of excitatory-inhibitory postsynaptic currents induced in cortical pyramidal neurons, leading to degradation of the phase-locking ability of pyramidal neurons in responding to repetitive stimuli and ultimately to degradation of rhythm perception in behavior. **Conclusion** These results in rodent model provide evidence that tiny millisecond-level changes in excitatory-inhibitory integration of cortical synaptic networks caused by early acoustic experiences are sufficient to degrade the rhythm perception in adult individuals.

Disclosures: Y. Sun: None. **Y. Zhang:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.14/AA28

Topic: D.05. Auditory & Vestibular Systems

Title: Investigating the neuronal response of the auditory thalamus

Authors: *B. KIM, H. JEONG, E. CHEONG;
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Abstract: The ability to process a wide array of auditory information is crucial for the animals as it directly relates to survival in an environment filled with diverse sound stimuli. One of the main components of the auditory pathway is the lemniscal pathway, which transmits sound information originating from the cochlear to the primary auditory cortex (A1). This transfer of sound stimuli involves sequential passage through various structures including the cochlear nucleus, superior olivary complex, inferior colliculus (IC), and medial geniculate nucleus of the thalamus (MGN). Neurons within these structures are known to display a tonotopic arrangement, where their spatial distribution correlates with responsiveness to specific frequencies. Interestingly, some of the A1 neurons also demonstrate response towards diverse characteristics of sound, such as timing and frequency change gradients. Ventral MGN, one of the components of the lemniscal pathway, receives inputs from central nucleus of IC, both of which exhibit this tonotopic arrangement. However, our understanding of the neuronal responsiveness of auditory thalamus in living animals remains incomplete. In this study, we fill this gap by presenting the activity of MGv neurons of living mice by the extracellular single-unit recordings *in vivo* using Neuropixels probes.

Disclosures: B. Kim: None. **H. Jeong:** None. **E. Cheong:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.15/BB1

Topic: D.05. Auditory & Vestibular Systems

Support: NSF Award 2124705

Title: Ecog gamma-band modulations induced by word vs tone categorization task show distinct spatio-temporal pattern in the temporal lobe.

Authors: *I. TASNIM[1], P. ASMAN[2], C. SWAMY[2], M. HALL[2], G. PELLIZZER[3,4], K. NOLL[5], S. TUMMALA[5], S. PRABHU[6], N. F. INCE[2];
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Abstract: Temporal dynamics of functional brain activity during processing of different auditory and linguistic components are not well characterized. To better understand the neural language processing, it is important to investigate the effect of different types of auditory stimuli on the patterns of propagation of cortical activations. We studied ECoG gamma-band modulations induced by different auditory tasks. Five subjects (two females and three males, age 34~64 years) with left temporal lobe glioma underwent resection involving awake language mapping, using a 4x8 ECoG electrode grid with 1cm pitch. Tasks included verbally responding to single word vs tone categorization (stimulus duration 300~500ms), and sentence level auditory naming

(AN) task (stimulus duration > 1s). High gamma-band (50~300Hz) modulations in superior and middle temporal gyri (STG, MTG) were induced by words and tones across all subjects, with distinct spatio-temporal patterns for each stimuli type. Both types of stimuli induced modulations as early as 100~200ms post stimuli-onset, word-induced modulations lasted longer (> 500ms) compared to tone. Word-induced modulations propagated from posterior to anterior temporal lobe, had larger spatial spread and late (> 200ms post onset) activated regions in the posterior MTG, compared to tone-induced posterior modulations. This indicates the association of anterior temporal regions with semantic processing. Spatio-temporal pattern of cortical modulations by word stimuli and the AN task were similar. This study shows that neural processing of auditory stimuli with and without linguistic components differs in activated cortical regions as well as in temporal dynamics.

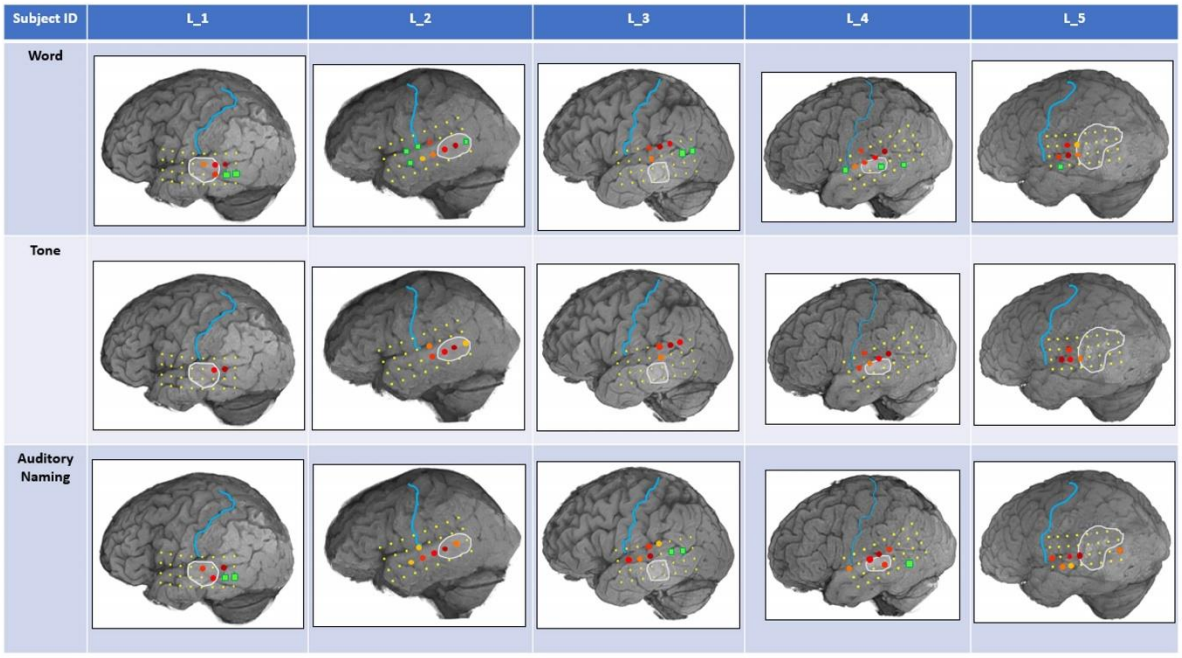

Figure: ECoG high-gamma band (50~300Hz) activation profile induced during different auditory processing tasks, across five subjects. 3D cortical brain mesh from patient-specific pre-operative MRI scans, tumor regions (grey curve) and central sulcus (cyan) are marked. Electrode contacts (small yellow dots), task-specific high-gamma modulated contacts (larger circles; signal propagation denoted by color gradient: from red to orange) and late activated contacts (green squares) are also marked.

Disclosures: I. Tasnim: None. **P. Asman:** None. **C. Swamy:** None. **M. Hall:** None. **G. Pellizzer:** None. **K. Noll:** None. **S. Tummala:** None. **S. Prabhu:** None. **N.F. Ince:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.16/BB2

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grants R01 DC015232
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UC Davis Departmental Funds

Title: Evidence for parallel processing of temporal and spatial information in the primate auditory cortex at single neuron resolution in a behaving macaque monkey

Authors: *D. LU, J. S. JOHNSON, K. L. SISSON, M. STROUD, K. NEVERKOVEC, K. STEWART, J. ROBERTS, G. H. RECANZONE;
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Abstract: Auditory cortical processing in primates has been proposed to be divided into at least two parallel processing streams, a caudal spatial stream and a rostral non-spatial stream. Whereas functional imaging studies in humans have supported this hypothesis, few studies have investigated neural processing at the single-cell level in the auditory cortex of nonhuman primates. Therefore, we recorded single neurons from auditory cortex while an adult male macaque monkey was performing a two-alternative forced choice task to discriminate either the modulation frequency or the spatial location of a broadband amplitude-modulated noise on alternating blocks of trials. Stimuli were 500ms duration, 65 dB SPL, 100% modulation depth broadband noise presented from 90 - 170 degrees approximately 1 m from the center of the monkey's head. The macaque was trained to initiate a trial by moving a joystick to the left. The first stimulus (S1) was modulated at either 17 or 34 Hz, presented from 130 degrees, followed by the second stimulus (S2) 500 ms after the offset of the S1. In the temporal task, the modulation frequency of the S2 varied from the S1 by +/- 1 octave in 7 equal octave steps, and it was presented from the same speaker as S1. For the spatial task, the same stimulus as the S1 was presented from +/- 40 degrees in 8 degree steps. The monkey was required to move the joystick in one of two directions to indicate that it perceived the S2 as either at a higher or lower rate than the S1 in the temporal task, or to the left or right of the S1 in the spatial task. We recorded single neuron activity from the contralateral primary auditory cortex (A1; n = 113), the caudolateral field (CL; n = 19), the caudomedial field (CM; n = 49) and the rostral field (R; n = 113). We calculated the firing rate (FR) and the vector strength (VS) of each neuron from 70-500 ms from each S2 onset. We also calculated the linear regression of each neuron across S2 stimuli for both the temporal and spatial tasks for both FR and VS. Finally, we calculated the dynamic range, defined as: (max-min)/(max+min) across S2 stimuli in each task. In the temporal task, we found that neurons in all four areas had equivalent FR tuning. However, based on the VS, neurons in area R had the best tuning and those of CL the worst. In the spatial task, neurons in area CL had the best FR tuning with the other three areas having equivalently worse tuning. Tuning based on the VS was equivalent across neurons in all four areas. These results provide good evidence in support of parallel processing of temporal and spatial information in the primate auditory cortex at the single neuron level.

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Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

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Program #/Poster #: PSTR273.17/BB3

Topic: D.05. Auditory & Vestibular Systems

Support: R01DC012947
R01DC019979

Title: Flexible tracking of rhythmic acoustic streams in parallel thalamocortical circuits

Authors: C. A. MACKEY[1], A. BARCZAK[1], S. NEYMOTIN[1], K. MACKIN[1], T. M. MCGINNIS[1], T. A. HACKETT[2], P. LAKATOS[1], C. E. SCHROEDER[3], *M. O'CONNELL[4,1]; [1]Nathan Kline Inst., Orangeburg, NY; [2]Hearing & Speech Sciences, Psychology, Vanderbilt Univ., NASHVILLE, TN; [3]Nathan Kline Inst. - Translational Neurosci. Div., Columbia Univ. Col. of Physicians and Surgeons, Orangeburg, NY; [4]Nathan S Kline Inst., Orangeburg, NY

Abstract: The natural world is replete with acoustic signals displaying varying degrees of periodicity, such as speech. The auditory system's ability to track periodicity via oscillatory entrainment of the local field potential (LFP) has been well documented in humans and nonhuman animals, with animal models providing critical insight into the laminar circuitry involved. However, animal studies typically use periodic stimuli, while natural stimuli such as speech are "quasi"-periodic; and humans readily comprehend time-compressed speech. Tolerance for quasi-periodicity and time compression suggest speech processing is highly flexible, however, much remains to be discovered about the underlying circuitry. Our previous work suggests that distinct cortical layers, and their thalamic inputs, play different roles in the entrainment process. "Matrix" (nonlemniscal) thalamic inputs targeting supragranular layers provide a modulatory influence on the processing of narrowly tuned information that is conveyed to the granular layer from the "core" (lemniscal) thalamus. This leads us to hypothesize that tracking of more naturalistic, quasi-rhythmic auditory stimulus streams may differ across core and matrix thalamocortical circuits. To test this hypothesis, we evaluated the degree to which neuronal activity in macaque primary auditory cortex (A1) and medial geniculate body (MGB) tracks or entrains to 40 dB SPL band-pass noise that was progressively jittered around presentation rates (1.6 Hz, Delta; 6 Hz, Theta; 11 Hz, Alpha). We analyzed LFPs (via current source density for cortex, and bipolar field potential for thalamus) and multi-unit activity. Entrainment was quantified using intertrial coherence (ITC), measuring the consistency of LFP phase across trials. For each recording site, ITC was used to estimate entrainment's "tolerance for" or robustness to jitter and its flexibility across different repetition rates. Across core and matrix circuits, entrainment decreased as jitter increased, and the tolerance for jitter decreased as presentation rate increased. The supragranular layers of A1 exhibited greater flexibility than the granular and infragranular layers in that their entrainment suffered less from increasing presentation rate. Consistent with this, at the highest presentation rate (11 Hz), matrix MGB exhibited greater tolerance for jitter than core MGB. These results suggest that parallel core and matrix thalamocortical circuits may have different roles in tracking patterns present in natural sounds. Future analyses will incorporate spiking activity and modulatory influences, like attention and eye movements.

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Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.18/BB4

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R00DC016046
NIH Grant R01DC020742

Title: Orbitofrontal cortex shapes auditory cortical and perceptual sensitivity

Authors: *M. MACEDO-LIMA, L. S. HAMLETTE, M. L. CARAS;
Biol., Univ. of Maryland Col. Park, College Park, MD

Abstract: Sensory acuity can benefit from practice, through which we can improve our ability to see, hear, smell, and taste - a process termed perceptual learning. In the auditory system, perceptual learning supports the development of speech and musicality and improves speech recognition in the hearing-impaired. Non-sensory processes, like attention or reward, make critical contributions to perceptual learning, but the neural circuits and mechanisms that mediate their involvement are poorly understood. The orbitofrontal cortex (OFC) has well-established roles in signaling reinforcement and in transmitting state-dependent feedback via direct projections to auditory cortex. We hypothesized that OFC neurons provide non-sensory input to the auditory cortex that supports auditory perception and perceptual learning. If OFC transmits a non-sensory signal to the auditory cortex that shapes auditory cortical sensitivity and perception, then silencing OFC activity should disrupt auditory cortical sensitivity and impair behavioral sound detection. To test this prediction, we used muscimol (a GABAa agonist) to inactivate bilateral OFC, and simultaneously recorded extracellular responses from auditory cortical neurons in freely moving Mongolian gerbils of both sexes as they performed an amplitude modulation (AM) detection task. We found that inactivation of bilateral OFC significantly impaired both behavioral and neural AM detection. Next, we asked whether OFC neurons exhibited learning-related changes in activity by using chronically implanted electrode arrays to record from OFC neurons as gerbils trained on an auditory perceptual learning task with progressively more challenging AM stimuli. We found that the firing rates of OFC neurons gradually increased and correlated with the degree to which perceptual thresholds improved. To determine whether learning affected the specific subpopulation of OFC neurons that innervate the auditory cortex, we used fiber photometry to record calcium signals from just the OFC neurons that project to the auditory cortex as gerbils underwent auditory perceptual learning on the same task. We found that calcium signals in these cells grew larger as perceptual thresholds improved, suggesting that OFC neurons send progressively stronger signals to auditory cortex

over the course of perceptual learning. Our results support the hypothesis that the OFC facilitates practice-dependent improvements in perceptual and auditory cortical sensitivity via a direct projection to auditory cortex.

Disclosures: M. Macedo-Lima: None. **L.S. Hamlette:** None. **M.L. Caras:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.19/BB5

Topic: D.05. Auditory & Vestibular Systems

Title: Neural representation of auditory stimuli in misophonia tracks with subthreshold autistic phenotype

Authors: *A. AK[1], J. E. NORRIS[1], S. H. KIMBALL[2], L. E. ETHRIDGE[1,3];
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Abstract: Misophonia is a disorder in which one or more specific auditory stimuli cause an extreme emotional response. Individuals with misophonia may present with sensory symptoms similar to those below the threshold for autism spectrum disorder (ASD), where symptom severity of ASD-like symptoms may track across the entire spectrum. Thirty-seven undergraduate students (18-22; M age = 18.89, SD = 0.99, 19 individuals with misophonia, 18 individuals without misophonia) from the University of Oklahoma completed a self-report spectrum characteristics survey indexing misophonia and the broad autism phenotype questionnaire (BAPQ). They also completed an audiology workup and participated in five tasks while undergoing 128 channel electroencephalography (EEG). The current study reports on results from the auditory chirp (white noise amplitude modulated by a sinusoid linearly increasing in frequency from 0 to 100 Hz over 2000ms) EEG task. Changes in neural responses to the chirp stimulus have been found in individuals with ASD and related developmental disorders. Misophonic individuals self-reported significantly increased autistic traits across all BAPQ sub-scales compared to controls: aloof: $t(34) = -2.23$, $p = .033$, d = -.74; pragmatic language: $t(34) = -2.25$, $p = .031$, d = -.75; rigid: $t(34) = -2.90$, $p = .007$, d = -.97. Additionally, a significant correlation was found between misophonia symptoms severity from audiology and the rigid subscale score (r = .33, $p = .048$). Log transformed phase-locking in the low gamma frequency range to the chirp stimulus was marginally lower for the misophonia group compared to controls, t(34)= 1.97, p=.058, d=.66. Log-transformed phase locking in the high gamma frequency range was significantly correlated across groups with increased autistic traits for both pragmatic language (r = .35, $p = .045$) and aloof (r = .36, $p = .035$) subscale scores. Individuals with misophonia exhibit a subthreshold autistic phenotype which shares a complex relationship with sensory processing-related neural activity in the gamma range. Reductions in

low gamma phase-locking to the chirp stimulus reflect an auditory phenotype similar to that found in ASD and related developmental disorders, which may reflect shared biology.

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Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.20/BB6

Topic: D.05. Auditory & Vestibular Systems

Support: NIH RO1DC017785 (POK)

Title: Increased interactions between harmonic-neurons & broadly-tuned neurons contributes to the increased selectivity to more spectrally complex stimuli in L2/3 of mouse secondary auditory cortex

Authors: *Y. CHEN, P. O. KANOLD;
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Abstract: Harmonics, universally found in vocalization, plays a vital role in daily life of human and other species to perceive their surroundings. Harmonics can be composed of one or more frequencies that are integer multiples of a fundamental frequency. Higher order auditory cortical areas such as L2/3 of secondary auditory cortex (A2) are thought to be preferentially activated by vocalizations and artificial harmonics complexes. Sound evoked responses emerge in the primary auditory cortex (A1) and A1 L2/3 neurons can already be highly selective to features of vocalizations. Since a transformation of the neural representation of sound features occurs between A1 L4 and A1 L2/3, the selectivity for vocalization features might emerge in a hierarchical manner between A1 L4 and A2. Here we use in vivo two photon calcium imaging to image L2/3 and L4 of A1 and L2/3 A2 of CBA;thy1GCaMP6s transgenic mice to study the neural representation of simple and complex harmonics in terms of number of components, and to identify differences of neural representations in A1 L4, A1 L2/3, and A2 L2/3. We find that neurons responding to only harmonics are present in both A1 and A2. However, while A1 shows a similar fraction of neurons responding to harmonic sounds with one or more components, A2 shows higher fraction of responding neurons when more complex harmonics are presented. These results indicate a progressively increasing selectivity for more spectrally complex stimuli from A1 to A2. Imaged neurons are grouped based on their response to sounds into: HN (only harmonics), PTN (only pure tones), and HPTN (harmonics and pure tone components). Most of HPTNs respond to multiple harmonic sounds and their pure tone components, which indicates HPTNs are more broadly tuned. We found neurons of all categories in A1 and A2. To identify differences in functional connectivity between cell categories between areas, we calculated noise correlations. Noise correlations in HN-HN neuron pairs between harmonic and pure tone conditions in A1 and A2 are similar, indicating that intra-group communication among HNs

might not be necessary for A2 to construct its selectivity. In contrast, inter-group interaction of HN-HPTN in A2 L2/3 has significantly increased noise correlation to two-tone harmonic which is sustained in ten-tone harmonic compared to pure tone. A1 L2/3 shows significantly decreased HN-HPTN noise correlation only to ten-tone harmonic but not to two-tone harmonic. A1 L4 shows no significant difference in all three conditions mentioned above. These results suggest that A2 contains specific functional connectivity that might contribute to the high selectivity to more spectrally complex auditory stimuli.

Disclosures: Y. Chen: None. **P.O. Kanold:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.21/BB7

Topic: D.05. Auditory & Vestibular Systems

Support: ONRN00014-17-1–2736

Title: Specializations of bat auditory cortex for processing echoes arriving at different delays.

Authors: *S. MACIAS HERRERA[1], M. SMOTHERMAN[2];
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Abstract: The bat auditory system follows the standard mammalian plan, but many specializations have been uncovered that appear uniquely tailored to support echolocation. However, it still remains uncertain which, if any, neurophysiological specializations are truly unique to echolocation. The question is important because it defines the extent to which bats may serve as general models of auditory processing, and it points toward which elements are critical for biosonar processing. One of their most unique neurophysiological features is the presence of neurons sensitive to the time delay between the outgoing pulse and returning echo. These delay-tuned neurons are found in the auditory cortex of all bats, but their neuroanatomical distribution is distinctly different in FM-type bats compared to CF-type and neotropical fruit bats. In FM bats, delay-tuned neurons are sprinkled throughout the primary auditory cortex rather than comprising their own auditory subfield, suggesting they might do more than just target ranging. We hypothesized that delay-tuned neurons might dynamically modulate the neural substrate to match changing pulse acoustics for targets at different distances. Results supported the hypothesis by showing that activation of delay-tuned neurons was directly correlated with concomitant changes in the frequency-tuning properties of nearby neighboring neurons.

Disclosures: S. Macias Herrera: None. **M. Smotherman:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.22/BB8

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R01-DC04290
NIH Grant UL1-RR024979

Title: Encoding of musical features during naturalistic listening: an intracranial EEG study

Authors: *A. J. BILLIG[1], A. E. RHONE[2], K. V. NOURSKI[2], D. GRAY[1], J. I. BERGER[2], C. M. GARCIA[2], C. K. KOVACH[2], C. I. PETKOV[2], B. J. DLOUHY[2], H. KAWASAKI[2], M. A. HOWARD III[2], T. D. GRIFFITHS[3], M. STEINSCHNEIDER[4];
[1]Ear Inst., Univ. Col. London, London, United Kingdom; [2]Dept. of Neurosurg., The Univ. of Iowa, Iowa City, IA; [3]Biosci. Inst., Newcastle Univ., Newcastle upon Tyne, United Kingdom; [4]Dept. of Neurol., Albert Einstein Col. of Med., Bronx, NY

Abstract: Music is present in all human cultures, can evoke powerful emotional responses, and has potential in a range of therapeutic settings. Neural transformations from acoustic to higher-order representations possibly underlying these effects during naturalistic listening have rarely been studied with high spatiotemporal resolution. We used techniques from continuous speech modelling (Broderick et al, J Neurosci 2019 39:7564-75) to examine the contribution of different acoustic and musical features to responses throughout the human brain. Participants were 55 patients undergoing pre-surgical intracranial electroencephalography (iEEG) monitoring for epilepsy using cortical grids and depth electrodes. They listened passively to at least three pieces of Western classical and popular music. Following a study in mice (Martorell et al, Cell 2019 177:256-271), which found that 40 Hz click trains entrained hippocampal unit firing and reduced Alzheimer's disease-like pathology, we also presented a subset of participants with a 40 Hz sinusoidally amplitude-modulated version of one musical piece. Multivariate temporal response functions were derived from the iEEG data, relating the 1-8 Hz bandpass-filtered neural signal at lags of 0-600 ms to acoustic and musical stimulus features (envelope, rectified envelope derivative, spectrogram, key clarity and stability). Cross-validated prediction accuracies were tested against results from a null distribution obtained by permuting stimulus information. Stimulus envelope most strongly predicted responses in core auditory cortex within posteromedial Heschl's gyrus, with peaks in the temporal response function within 100 ms. In a subset of envelope-following sites at mostly superior temporal locations, the inclusion of onset and spectral information in the model explained additional response variance. Higher-level musical features (key clarity and stability) were most strongly represented at more anterior and medial temporal sites, including temporal pole, parahippocampal gyrus, and hippocampus. Encoding of these features was maximal at lags greater than 300 ms. For amplitude-modulated stimuli, 40 Hz iEEG power increased at widely distributed sites, and in the small number of participants with single unit data, firing in auditory cortex but not hippocampus aligned to particular phases of the 40 Hz cycle. Further unit data are being collected, while ongoing analysis extends the modelling to other neural frequency bands and examines effects of musical familiarity on response latency and connectivity between auditory and memory circuits.

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Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.23/BB9

Topic: D.05. Auditory & Vestibular Systems

Support: NSERC RGPIN-2022-04413
DGECR-2022-00294

Title: Neural tracking of speech and song is predicted by subjective ratings of rhythmic regularity

Authors: *C. M. V. B. DER NEDERLANDEN;
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Abstract: Rhythm is a key feature in communicative interactions, especially for vocal communication through speech and song. However, the way that rhythm unfolds in speech and song differs, where onsets in song occur on the beat and at integer multiples of the beat but not in speech. A large body of work characterizes how the brain tracks speech rhythms at the syllable rate (theta, 4-8 Hz), but how do the regular rhythms of song affect neural tracking of syllables when they are sung and spoken? In this jack-knifed reanalysis of MEG neural tracking data for speech and song (32 participants, 384 trials), independent subjective ratings of rhythmic regularity (51 participants, 96 trials) for each stimulus predict the degree of neural tracking (cerebro-acoustic phase coherence). Rhythmic regularity and pulse clarity predict unique variance in neural tracking, even when stimulus type (speech or song) is included in the model, suggesting that rhythmic regularity for speech and song drives neural tracking. Results will be discussed in the context of how the regular rhythmic features of song could be used to facilitate learning and memory.

Disclosures: **C.M.V.B. der Nederlanden:** None.

Poster

PSTR273. Auditory Processing: Temporal, Frequency, and Spectral Processing

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Topic: D.05. Auditory & Vestibular Systems

Support: R011DC016915
R01DC016765
R01DC017991
S10OD023637
R01DC016765
R01DC017915
R01DC017991
P41EB015896

Title: Mapping the intrinsic functional organization of auditory cortex in individuals using 7T MRI

Authors: *M. HAKONEN[1], L. DAHMANI[1], A. BLAZEJEWSKA[1], W. CUI[2], P. KOTLARZ[1], K. LANKINEN[1], M. LI[3], J. POLIMENI[1], J. REN[3], T. TURPIN[4], D. WANG[1], H. LIU[1], J. AHVENINEN[1];
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Abstract: Individual differences in behavior and cognition have been shown to be reflected in variability of functional connectivity. High individual variability may be one of the major factors why a widely accepted model of the human auditory cortex (AC), analogous to that in non-human primates, is still lacking. Due to the lack of a robust strategy for individual-level analysis, most neuroimaging studies on human AC have focused on group-level analyses to identify central tendencies that represent the typical brain. Another major challenge has been that the spatial resolution of the noninvasive neuroimaging methods is insufficient to localize small subareas of AC, many of which encompass only a few conventionally sized functional magnetic resonance imaging (fMRI) voxels. To overcome these challenges, we applied a novel highly reliable functional network parcellation strategy to localize fine-grained functional subareas of AC in individuals based on ultra-high-resolution data acquired by 7T MRI (1 mm^2 voxel size, N =30). All participants took part in at least three two-hour sessions on different days. Two of the sessions included resting state measurements and the remaining sessions auditory and audiovisual localizer tasks. The subareas of superior temporal cortex (STC) in or near auditory areas showed high within-subject reproducibility between the resting state measurements (Dice's coefficient: left: 0.78, right: 0.78). At the same time, these STC subareas revealed substantial inter-subject variability (Dice's coefficient: left: 0.68, right: 0.69). As expected, the intrasubject similarity was significantly higher than the inter-subject similarity ($p<0.001$), demonstrating that our approach is not only highly reproducible within individuals but also reliably and robustly captures meaningful individual variability. The inter-subject variability was also larger in AC than in the rest of the brain (Dice's coefficient: left: 0.81, right: 0.81, $p<0.001$). The parcellation results were consistent with a tonotopy map and an audiovisual interaction map determined using a general linear model analysis from task-based localizer data. Our results demonstrate that AC can be reliably segmented into functional subareas that substantially vary across individuals.

Disclosures: **M. Hakonen:** None. **L. Dahmani:** None. **A. Blazejewska:** None. **W. Cui:** None. **P. Kotlarz:** None. **K. Lankinen:** None. **M. Li:** None. **J. Polimeni:** None. **J. Ren:** None. **T. Turpin:** None. **D. Wang:** None. **H. Liu:** None. **J. Ahveninen:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR274.01/BB11

Topic: D.05. Auditory & Vestibular Systems

Support: NIH NIGMS R35GM138023
White Hall Foundation Research Grant

Title: Effects of vesicular zinc signaling on parvalbumin interneurons in the mouse auditory cortex

Authors: *H. A. BOYD-PRATT[1], P. T. R. BENDER[2], C. T. ANDERSON[3];
[2]West Virginia Univ. - Neurosci. Grad. Program, [1]West Virginia Univ., Morgantown, WV;
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Abstract: Auditory processing in the auditory cortex relies on precisely organized circuits consisting of discrete inhibitory and excitatory neurons in different cortical layers. Parvalbumin (PV)-positive interneurons, the most common type of inhibitory neuron in the sensory cortex, provide inhibitory control of cortical function through their synaptic connections with local excitatory neurons.
ZnT3 is a zinc transporter protein that loads free zinc into glutamatergic vesicles where it is coreleased with glutamate and shapes the function of NMDA and AMPA receptors. This synaptic zinc is a powerful modulator of synaptic signaling and supports the processing of acoustic stimuli. Recently, research has uncovered cell-type and synapse-specific roles of synaptic zinc signaling, but the synaptic mechanisms by which vesicular zinc shapes the activity of inhibitory interneurons is not well understood.
Understanding the role of synaptic zinc and ZnT3 in specific excitatory-inhibitory circuits addresses a significant gap in our understanding of the mechanisms underlying the synaptic basis of inhibitory control crucial for precise acoustic encoding. We used optogenetic activation and simultaneous paired whole-cell patch-clamp electrophysiological recordings in acute brain slices from PV-Cre mice to determine the synapse-specific effects of synaptic zinc on excitatory-inhibitory microcircuits in the auditory cortex of mice.

Disclosures: H.A. Boyd-Pratt: None. **P.T.R. Bender:** None. **C.T. Anderson:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

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Program #/Poster #: PSTR274.02/BB12

Topic: D.05. Auditory & Vestibular Systems

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NIH Grant P30GM103503
NIH Grant U54GM104942
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WVU Cancer Insititute

Title: Trans-synaptic relationship between vesicular zinc and Shank3 supports dendritic spine structure and function

Authors: *A. MANNING, P. T. R. BENDER, H. BOYD-PRATT, M. HRUSKA, C. T. ANDERSON;
Neurosci., West Virginia Univ., Morgantown, WV

Abstract: Mutations in the gene that encodes for Src homology 3 and multiple ankyrin repeat domains protein 3 (Shank3) result in altered synaptic function and morphology. Shank3 is a synaptic scaffolding protein that assists in tethering and organizing proteins and glutamatergic receptors in the postsynaptic density of excitatory synapses, thereby supporting normal synaptic function. The localization of Shank3 to excitatory synapses and the formation of stable Shank3 sheets is regulated by the binding of zinc to the C-terminal sterile-alpha-motif (SAM) domain of Shank3. Disruptions of zinc in synapses that are enriched with Shank3 leads to a loss of postsynaptic proteins important for synaptic transmission, suggesting that zinc supports the localization of postsynaptic proteins via Shank3. The brain is highly enriched with free zinc inside glutamatergic vesicles at presynaptic terminals. Zinc transporter 3 (ZnT3) moves zinc into vesicles where it is co-released with glutamate. Alterations in ZnT3 are implicated in multiple neurodevelopmental disorders, and ZnT3 knock-out (KO) mice - which lack synaptic zinc - show behavioral deficits associated with autism spectrum disorder and schizophrenia. Here we show that ZnT3 KO mice have smaller dendritic spines and mini excitatory postsynaptic current amplitudes than WT mice. Additionally, spines with Shank3 are smaller in ZnT3 KO mice compared to WT mice, and synapses with both Shank3 and ZnT3 have larger spines in WT mice compared to synapses with only Shank3. Together these findings suggest a mechanism whereby presynaptic zinc supports normal postsynaptic structure and function via Shank3.

Disclosures: A. Manning: None. **P.T.R. Bender:** None. **H. Boyd-Pratt:** None. **M. Hruska:** None. **C.T. Anderson:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

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Program #/Poster #: PSTR274.03/BB13

Topic: D.05. Auditory & Vestibular Systems

Support: NIGMS T32-GM133369
NIGMS T32-GM132494
NIGMS R35-GM138023
Whitehall Foundation: 2020-05-44

Title: Synaptic zinc potentiates AMPA receptor function in mouse auditory cortex

Authors: *P. T. R. BENDER, M. MCCOLLUM, H. BOYD-PRATT, B. Z. MENDELSON, C. T. ANDERSON;
Neurosci., West Virginia Univ., Morgantown, WV

Abstract: Synaptic zinc signaling modulates synaptic activity and is present in specific populations of cortical neurons, suggesting that synaptic zinc contributes to the diversity of intracortical synaptic microcircuits and their functional specificity. To understand the role of zinc signaling in the cortex, we performed whole-cell patch-clamp recordings from intratelencephalic (IT)-type neurons and pyramidal tract (PT)-type neurons in layer 5 of the mouse auditory cortex during optogenetic stimulation of specific classes of presynaptic neurons. Our results reveal that synaptic zinc potentiates AMPAR function in a synapse-specific manner. We performed in vivo 2-photon calcium imaging of the same classes of neurons in awake mice and found that changes in synaptic zinc can widen or narrow the sound-frequency tuning bandwidth of IT-type neurons, but only widen the tuning bandwidth of PT-type neurons. These results expand the known functions of synaptic zinc and reveal synapse- and cell-type specific actions of synaptic zinc in the cortex.

Disclosures: P.T.R. Bender: None. **M. McCollum:** None. **H. Boyd-Pratt:** None. **B.Z. Mendelson:** None. **C.T. Anderson:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

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Program #/Poster #: PSTR274.04/BB14

Topic: D.05. Auditory & Vestibular Systems

Support: NIH NIGMS T32 GM132494
NIH NIGMS R35GM138023
Whitehall Foundation Research Grant

Title: Cell-type specific enhancement of deviance detection by synaptic zinc in mouse auditory cortex

Authors: *M. MCCOLLUM[1], A. MANNING[2], C. T. ANDERSON[3];
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Abstract: A fundamental feature of sensory processing is the ability of animals to adapt to the current conditions in their environment yet maintain their ability to detect novelty in the same environment. A correlate of this ability is a robust neuronal phenomenon called stimulus-specific adaptation, in which a repeated stimulus will result in adaptation with smaller and smaller neuronal responses over time, but a deviant stimulus will still elicit larger robust responses from the same neurons. Recent work has established that synaptically released zinc is an endogenous mechanism that shapes neuronal responses to sounds in the auditory cortex. Here, to understand the contributions of cortical synaptic zinc to deviance detection of specific cortical neurons we performed wide field and 2-photon calcium imaging of multiple classes of cortical glutamatergic neurons. We find that intratelencephalic (IT) neurons in both layer 2/3 and layer 5 as well as extratelencephalic (ET) neurons in layer 5 all demonstrate deviance detection, however, we find a specific enhancement of this deviance detection in ET neurons that arises from ZnT3-dependent synaptic zinc from layer 2/3 IT neurons. Genetic deletion of ZnT3 from layer 2/3 IT neurons removes the enhancing effects of synaptic zinc on ET neuron deviance detection and also results in poorer acuity of detecting deviant sounds by behaving mice.

Disclosures: M. McCollum: None. **A. Manning:** None. **C.T. Anderson:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR274.05/BB16

Topic: D.05. Auditory & Vestibular Systems

Title: Exploring the Role of Tonic GABA in Mouse Auditory Thalamus

Authors: *Y. CHO, E. CHEONG;
Yonsei Univ., 50, Yonsei-ro, Seodaemun-gu, Seoul, Korea, Republic of

Abstract: Sound perception is crucial for animals' survival, enabling them to localate and identify sound sources. The auditory pathway, beginning at the ear, culminating at the cortex, involves several critical stages. One of these stages includes the transmission of auditory signals through medial geniculate nucleus (MGN) in the thalamus, an important sensory relay station within the auditory thalamus, forwarding it to auditory cortex. The MGN itself is divided to three different subdivisions based on their anatomical location, MGv (ventral), MGd (dorsal), and MGm (medial). These subdivisions have unique connective inputs from inferior colliculus (IC), and each of the pathway reflects subdivision-specific connections from IC to MGN, and thus has different roles in auditory processing. MGv is responsible for primary sound representation, MGd is associated with secondary and more complex sound representation, and MGm is

responsible for multi-modal sensory processing. We previously reported that tonic GABA current in the thalamus plays a critical role in modulating sensory processing. However, the function of tonic inhibition in auditory processing, particularly within the MGN subdivisions, has not been fully understood yet. Thus we explore tonic GABA current in various MGN subdivisions via *ex vivo* electrophysiology.

Disclosures: Y. Cho: None. **E. Cheong:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

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Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R01DC018353
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Amelia Peabody Scholarship
Harvard Center on the Developing Child Science and Innovation Fellowship

Title: Vasoactive Intestinal Peptide Signaling within Auditory Cortex

Authors: *C. LIU[1,3], C. G. SWEENEY[2,3], C. P. MACGREGOR[3], L. G. VATTINO[2,3], K. SMITH[3], A. E. TAKESIAN[3,1,2];
[1]Grad. Program in Speech and Hearing Biosci. and Technol., [2]Otolaryngology Head and Neck Surgery, Harvard Med. Sch., Boston, MA; [3]Eaton Peabody Labs., Massachusetts Eye and Ear, Boston, MA

Abstract: Identifying neural targets that control central auditory plasticity will have far-reaching impact, offering potential ways to restructure neural circuitry. Work from our lab and others have demonstrated that a group of cortical GABAergic neurons expressing vasoactive intestinal peptide (VIP) is important for sensory plasticity. Although many studies have leveraged the expression of VIP to genetically target this specific interneuron population, few have evaluated the function of the non-classical signaling molecule VIP in sensory processing and plasticity. We used a GPCR-Activation-Based (GRAB) peptide sensor and *in vivo* fiber photometry to study the release of VIP in mouse auditory cortex (ACtx) during passive sound presentation and associative auditory learning. Sound stimuli elicited VIP sensor responses in ACtx from a subset of mice. Furthermore, as mice learn to associate specific sounds with reward, VIP release may be modulated by the behavioral relevance of the sound stimuli. These experiments represent the first effort to study the *in vivo* release of VIP within sensory cortices. Parallel experiments are evaluating the postsynaptic effects of VIP release in ACtx. We first used *in situ* hybridization to quantify the expression levels of mRNA encoding the VIP receptor 1, *Vipr1*, across ACtx. Consistent with previous studies in other sensory cortices, we found that *Vipr1* is expressed

within 77% of excitatory pyramidal cells, marked by expression of vesicular glutamate transporter 1 (*Slc17a7*) and 18% of GABAergic neurons, marked by expression of the GABA synthesizing enzymes *Gad1* and *Gad2*. Ongoing studies are using *in vitro* electrophysiology to determine the functional postsynaptic effects of VIP receptor 1 activation. Together, these results may elucidate the effects of VIP within auditory cortical circuits, laying the necessary foundation for future loss- and gain-of-function experiments to evaluate the function of VIP release in auditory perception and learning.

Disclosures: C. Liu: None. **C.G. Sweeney:** None. **C.P. MacGregor:** None. **L.G. Vattino:** None. **K. Smith:** None. **A.E. Takesian:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR274.07/BB18

Topic: D.05. Auditory & Vestibular Systems

Support: DFG SPP 1608

Title: The two-pore potassium channel subunit Task5 regulates central auditory processing

Authors: *C. KÖRBER[1], H. SABER[2], M. KAISER[2], L. RÜTTIGER[3];
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Abstract: Processing of precisely timed auditory signals critically depends on the neuron's ability to fire brief action potentials (APs) at high frequencies and high fidelity for prolonged times. Many neurons perceiving information about the timing of signals fire a single AP at the be-ginning of the stimulus (onset firing), when stimulated in vitro. This firing pattern depends on brief APs as well as on the tight regulation of the neuronal excitability, which in turn de-pends on the expressed set of ion channels as well as the resting membrane potential (RMP). The RMP is determined by the ion channels open in the absence of an AP. Among these channels, two-pore potassium channels (K2P channels) play a key role as they contribute a large part of the potassium conductance at rest. The K2P subunit Task5 is expressed almost exclusively in the auditory brainstem nuclei. However, since it failed to form functional ion channels in heterologous expression systems, its function remined elusive. Here we show, using shRNA-mediated knock-down (KD) of Task5, that Task5 takes part in regulation of establishment of precisely timed, brief APs and onset firing pattern. Moreover, we demonstrate that Task5 knock-out (KO) mice show deficits in high frequency, high fidelity synaptic transmission at the endbulb of Held synapse in the cochlear nucleus of the auditory brainstem and in the processing of loud sounds.

Disclosures: C. Körber: None. **H. Saber:** None. **M. Kaiser:** None. **L. Rüttiger:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

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Topic: D.05. Auditory & Vestibular Systems

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NIH Grant T32 DC000011
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Rackham Graduate Student Research Grant

Title: GluN2D-containing NMDA receptors enhance temporal integration in VIP neurons in the inferior colliculus

Authors: *A. C. DROTOS, Y. N. HERRERA, R. L. ZARB, M. T. ROBERTS;
Dept. of Otolaryngology, Univ. of Michigan, Ann Arbor, MI

Abstract: Along the ascending auditory pathway, there is a broad shift from temporal coding, which is common in the lower auditory brainstem, to rate coding, which predominates in auditory cortex. This temporal-to-rate transition is particularly prominent in the inferior colliculus (IC), the midbrain hub of the auditory system, but the mechanisms that govern how individual IC neurons integrate information across time remain largely unknown. However, previous work has suggested that NMDA receptors (NMDARs) may play a role in this transition. NMDA receptors are critical components of most glutamatergic circuits in the brain, and the diversity of NMDA receptor subtypes yields receptors with a variety of functions. Here, we report that mRNA for the *GluN2D* NMDAR subunit is widely expressed in the IC, which is unusual as this subunit is typically expressed only early in development. Additionally, GluN2D-containing NMDARs are relatively insensitive to voltage-dependent Mg^{2+} block, and thus can activate at resting membrane potential in the absence of AMPA receptor activation. By using whole-cell electrophysiology combined with optogenetics and pharmacology, we show that GluN2D-containing NMDARs are activated at resting membrane potential in some IC neurons via inputs from the anteroventral cochlear nucleus (AVCN) and via inputs from the contralateral IC through the IC commissure. GluN2D-containing NMDARs also have much slower kinetics than other NMDARs, and we found that GluN2D-containing NMDARs facilitate temporal summation for trains of optogenetic stimuli in IC neurons by prolonging the time window for synaptic integration. Currently, we are using a dynamic clamp to investigate how expression of different NMDAR subunits alters temporal summation. Our results suggest that GluN2C/D-containing NMDARs support the shift from temporal to rate coding in the auditory system by facilitating the integration of ascending inputs.

Disclosures: **A.C. Drotos:** None. **Y.N. Herrera:** None. **R.L. Zarb:** None. **M.T. Roberts:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

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Program #/Poster #: PSTR274.09/Web Only

Topic: D.05. Auditory & Vestibular Systems

Support: ICMR 51/1/2018/ANA/BMS

Title: Expression of Neurotrophins (BDNF and NT-3) and their Receptors Across Ageing Adult Human Cochleae

Authors: *A. MISHRA[1], T. G. JACOB[1], T. C. NAG[1], A. YADAV[2], T. S. ROY[3];
[1]Anat., [2]Forensic Med. and Toxicology, AIIMS New Delhi, New Delhi, India; [3]Anat., North DMC Med. Col. and Hindurao Hosp., New Delhi, India

Abstract: Background:
Over 5% of the world requires rehabilitation for sensorineural hearing loss. It encompasses pathologies of the inner ear and auditory nerve. SNHL's definitive management is cochlear implantation, contingent on the presence of an adequate number of spiral ganglion neurons (SGNs) and hair cells. Age-related degeneration of these cells is a limiting factor in cochlear implant efficacy. Neurotrophins are keystones for the development and differentiation of SGNs, alongside maintaining synapses with the organ of Corti. BDNF and NT-3 are expressed in mice, rats, and chick cochleae at different stages of life, the experimental absence of which leads to deafness. Exogenous delivery of neurotrophins promotes SGN survival in deafened animals, indicating their probable therapeutic use for increasing the efficacy of cochlear implants. Studies on neurotrophin expression in adult human cochleae are lacking.
Methods:
Post ethical clearance, twelve human temporal bones containing cochlea and auditory nerve were derived within 24 hours of death. Bones were fixed in 4% paraformaldehyde, decalcified with 10% EDTA for twelve weeks, cryoprotected, mounted, and sectioned at 40µm on a cryotome to obtain coronal sections of the cochlea. Cryosections were used for studying the expression of BDNF, NT-3, and their receptors using immunohistochemistry. Antigens were retrieved using heat shock in citrate buffer (0.01M, pH 6), blocked in normal serum, quenched in 5% hydrogen peroxide, and incubated in primary antisera followed by species-specific secondary antibodies. The avidin-biotin-peroxidase complex is used to amplify the signal. Antigen-antibody binding sites were visualized using 3,3-diaminobenzidine tetrahydrochloride.
Results:
BDNF and NT-3 expressed in SGNs and neuropil, showing membranous and cytoplasmic positivity. The apical layer of stria vascularis (SV) expressed distinct positivity among the three layers. SGNs expressed bipolar positivity for TrkB and TrkC. Entire SV stained positive for receptor proteins.
Conclusion:
It can be extrapolated that the apical layer of SV produces neurotrophins which act on cells

expressing TrkB/TrkC. Age-related changes concluded a random decline in older groups in this qualitative observational study.

Disclosures: **A. Mishra:** None. **T.G. Jacob:** None. **T.C. Nag:** None. **A. Yadav:** None. **T.S. Roy:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR274.10/BB20

Topic: D.05. Auditory & Vestibular Systems

Title: Transcriptomic and morphological markers of functional specialization in statoacoustic ganglion neurons of larval zebrafish

Authors: *S. SEMENOVA, G. MARGOLIN, H. BURGESS;
NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Rockville, MD

Abstract: Sensory neurons associated with the inner ear of zebrafish receive multiple types of acoustic and vestibular input. Precise transgenic targeting of subpopulations of statoacoustic ganglion (SAG) neurons will facilitate functional decoding of central pathways for auditory processing. Therefore, we analyzed morphological and transcriptomic diversity of statoacoustic ganglion neurons in 6-day post-fertilization (dpf) larval zebrafish with the goal of identifying transcriptomic markers of structurally and/or functionally distinct groups of sensory neurons. Sparse transgenic labeling and morphological reconstruction of 228 SAG neurons revealed a topographic arrangement of cell bodies, where anteroposterior positioning of the neurons in the SAG reproduced the positioning of target hair cell patches, the sources of sensory input in the inner ear. Clustering of neuron traces based solely on central axon morphology showed that neurons that received peripheral input of the same type also projected to similar central targets. For example, axons of neurons that receive input from hair cell patches of the cristae associated with the semicircular canals were morphologically distinct from axons of utricle- and saccule-projecting neurons. Neurons that received input from the saccule were divided into four morphological subtypes based on axon branch length and symmetry. Three of these subtypes targeted restricted areas of the hair cell patch and thus may be selective for specific types of saccular input. As we observed neuron subpopulations forming “tracts” to connect specific hair cell groups to distinct brainstem targets, we set the goal to identify transcriptomic markers of these subpopulations. Using SmartSeq, we performed deep single cell RNAseq from 226 manually isolated 6 dpf SAG neurons. As expected, when merged with transcriptomic data from mouse sensory neurons, SAG neurons co-clustered with vestibular ganglion rather than spiral ganglion neurons. The degree of developmental maturity was the major factor that shaped SAG neuron transcriptomes: neurons from a population enriched in cristae-projecting cells were assigned to a cluster with high expression of developmentally regulated transcription factor genes (such as isl1 and tlx2) at 6 dpf, consistent with the idea that cristae-projecting neurons

become fully functional at late larval stages. Transcriptomic data also established differences in calcium handling and radial axon growth in neuron subgroups. Thus, SAG neuron subpopulations with distinct central and peripheral targets express unique molecular markers, paving the way for functional analysis through targeted transgenic lines.

Disclosures: S. Semenova: None. **G. Margolin:** None. **H. Burgess:** None.

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR274.11/BB21

Topic: D.05. Auditory & Vestibular Systems

Support: Eagles Autism Foundation

Title: Assessing Auditory Neural Responses in the Rett Syndrome Rat Model: A Comparative Analysis of Pre- and Post-Regression Responses

Authors: *Y. TAMAOKI, S. KROON, J. R. RILEY, C. T. ENGINEER;
Univ. of Texas at Dallas, Richardson, TX

Abstract: Title: Assessing Auditory Neural Responses in the Rett Syndrome Rat Model: A Comparative Analysis of Pre- and Post-Regression Responses**Authors**: Y. Tamaoki, S.L. Kroon, J.R. Riley, C.T. Engineer **Abstract**:Rett syndrome is a genetic disorder that is caused by a mutation in X-chromosome linked *Mecp2* gene. Individuals with Rett syndrome often exhibit seizures, impaired sociability, and difficulty in cognition, motor movements, and speech-language perception and production. These children initially develop seemingly typically, and regression symptoms occur at the age of 6 to 18 months. In the rodent model of Rett syndrome, similar regression symptoms, including impairments in sensory processing, become apparent starting from 4 months of age. Behaviorally, these heterozygous *Mecp2* rodents perform poorly on auditory discrimination tasks when background noise of varying intensities were present. These behavioral impairments are accompanied by degraded cortical activity patterns.. In the primary auditory cortex (A1), the tonotopic map that is normally organized from low to high frequencies are disrupted in *Mecp2* heterozygous rats. There is a shift in the tonotopic organization in which a greater representation of higher frequencies are observed. These findings have been documented in post-regression animals and nothing is known about auditory processing in pre-regression animals. Additionally, no studies have documented subcortical physiology in *Mecp2* animals. Therefore, the aims of this study are to 1) document multi-unit primary auditory cortex responses to sounds in heterozygous *Mecp2* rats before and after signs of regression are apparent and 2) investigate responses from the inferior colliculus in both pre-regression and post-regression rats. Neural responses evoked by tones, speech sounds, and click sounds were recorded from the primary auditory cortex and the inferior colliculus in heterozygous *Mecp2* rats and age-matched littermate control wild-type rats. Our preliminary

results suggest that responses to sounds in the inferior colliculus are also degraded in post-regression *Mecp2* rats. Surprisingly, pre-regression *Mecp2* rats also exhibit degraded responses to sounds in the primary auditory cortex. Insights derived from this study may expand the current understanding of auditory processing in Rett syndrome and other neurodevelopmental disorders.

Disclosures: Y. Tamaoki: None. **S. Kroon:** None. **J.R. Riley:** None. **C.T. Engineer:** Other; Married to an employee of Microtransponder Inc..

Poster

PSTR274. Auditory Processing: Neurotransmitters, Channels and Synapses

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Topic: D.05. Auditory & Vestibular Systems

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Natural Sciences and Engineering Council of Canada (NSERC) Discovery grant
Canadian Institutes of Health Research (CIHR) CGS-D

Title: Investigating histological changes in startle-mediating neurons in the brainstem of Cntnap2 knock-out rats

Authors: *A. ZHENG[1], C. DE OLIVEIRA[2], B. L. ALLMAN[2], S. SCHMID[1];
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Abstract: Mutations in the contactin-associated protein-like 2 gene (*CNTNAP2*) are associated with various neurodevelopmental disorders in humans, most notably autism spectrum disorder (ASD). Previous studies from our lab have consistently found that *Cntnap2* knock-out (KO) rats, a genetic animal model of ASD, have increased auditory reactivity as measured through the acoustic startle response (ASR), paralleling auditory hypersensitivity observed in ASD. Gaining a better insight into the neural basis underlying increased acoustic startle in *Cntnap2* KO rats will allow us to better understand auditory hypersensitivity in autistic individuals. The brain region that mediates the ASR is the caudal pontine reticular nucleus (PnC). Through conducting extracellular *in vivo* electrophysiological recordings in the PnC, we previously found increased firing rates in response to startling sounds in *Cntnap2* KO rats compared with wildtype littermates. However, these PnC firing rate differences were more drastic between female wildtype and female *Cntnap2* KO rats, whereas increased behavioural ASR does not show sex-dependent effects. Thus, having increased PnC firing rates does not fully explain increased ASR in *Cntnap2* KO rats. We therefore investigated morphological and histological properties of startle-mediating neurons in the PnC, which are known as “giant neurons”. Through immunohistochemical labelling of cells, we found that the total number of PnC giant neurons was not different between wildtype (n = 8) and *Cntnap2* KO (n = 8) rats. Next, we activated PnC giant neurons by presenting the rats with 30 pulses of startling stimuli (20-ms pulses at 95 dB,

white noise, 5 minutes prior to perfusing). Brain sections were labelled with an antibody against phosphorylated cAMP response element binding protein (pCREB) to visualize which neurons were activated. *Cntnap2* KO rats had increased expression of pCREB in PnC giant neurons compared with wildtype littermates. Additionally, male rats had increased pCREB expression compared with female rats. The PnC giant neurons that expressed pCREB were larger in terms of soma area in *Cntnap2* KO rats compared with wildtype littermates. However, pCREB was also seen in PnC giant neurons from a few control rats that were not presented with startling stimuli. Future studies will investigate whether increased ASR in *Cntnap2* KO rats is indeed due to increased pCREB expression in giant neurons in response to startling stimuli or due to increased pCREB expression in giant neurons at rest. Overall, our findings indicate that electrophysiological and histological changes in the PnC contribute to increased acoustic startle in *Cntnap2* KO rats.

Disclosures: **A. Zheng:** None. **C. De Oliveira:** None. **B.L. Allman:** None. **S. Schmid:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.01/BB23

Topic: D.05. Auditory & Vestibular Systems

Support: Foundation pour l'Audition
Pasteur Roux-Cantarini Fellowship

Title: Code of silence: Encoding Information in neural activity and silence along auditory pathways

Authors: *A. BUCK[1], T. DUPONT[1,2], R. ANDREWS[1], O. POSTAL[1,3], J. BOURIEN[4], N. MICHALSKI[1,5], B. GOUREVITCH[1];
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Abstract: There has been a long debate as to whether the auditory system uses a rate or temporal code. But what if this problem has been ill-defined as an 'either or' rather than as combinatorial? Here we recorded responses to long random dynamic complex sounds from a large sample of neurons in the inferior colliculus (IC), auditory thalamus (MGB) and auditory cortex (AC) of awake mice in addition to simulating responses in a biophysical model of the auditory nerve. We then quantified the amount of stimulus information carried by the firing rate, temporal patterns and neural silence (resting state of the neuron). We confirmed that stimulus information carried by individual neurons as well as information redundancy within populations of neurons decreases along ascending auditory pathways regardless of the encoding strategy used. We observed that maximum information reached by neurons was progressively transitioning from temporal encoding to encoding in the firing rate along the ascending auditory pathway. We

showed that periods of neural silence contain a significant amount of stimulus information, especially in subcortical areas, and therefore should be considered as part of neural encoding. Importantly, our observations from all auditory areas show the amount of information carried by a given code heavily depends on a given neuron's firing characteristics. These results suggest that both silent and active patterns of neural responses are relevant for information encoding further implying a multitude of encoding strategies co-existing at each level of the auditory system.

Disclosures: A. Buck: None. **T. Dupont:** None. **R. Andrews:** None. **O. Postal:** None. **J. Bourien:** None. **N. Michalski:** None. **B. Gourevitch:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

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Support: Fondation pour l'Audition
Institut Pasteur PTR
Institut Pasteur PRC

Title: Neural entrainment myth: Is 40 Hz special in mice?

Authors: *B. GOURÉVITCH, N. GONÇALVES, A. BUCK, C. DE CAMPOS PINA, T. DUPONT, N. MICHALSKI, L. ARNAL;
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Abstract: Brain activity synchronizes with sensory input rhythms through neural entrainment. This seems to be particularly important for auditory perception and can even be enhanced when the stimulus amplitude modulation rate corresponds to the time constant of activated neural circuits. For nearly half a century we have known that there is an increased response in the human EEG and MEG response to a stimulation rate of 40Hz in the auditory system, a phenomenon dubbed as the 40Hz auditory steady state response (ASSR) in the literature. Mechanisms remain unclear and would involve Parvalbumin positive interneurons. Importantly, the 40Hz ASSR has been identified as a marker of neurological health with multiple studies demonstrating its decreased prevalence in many neurological disorders. Thus, the 40Hz ASSR gained importance and was quickly adopted in rodents and especially mice models as a functional marker for brain disorders. However, does the enhanced neural entrainment at 40Hz even exist in mice? To answer this we went back to the compound and local neural activity in anesthetized and awake mice that we've recorded for years in the auditory pathways. We show that there is only a small enhancement of response amplitudes at 40Hz rhythms in the inferior colliculus, auditory thalamus (MGB) and auditory cortices of mice. This enhancement is robust to anaesthesia, but is more prevalent at the subcortical levels. These results bring into question

the specific role this frequency plays in the brain, and whether mouse is a valuable animal model for relating the 40Hz ASSR to the presence of neurological pathologies.

Disclosures: B. Gourévitch: A. Employment/Salary (full or part-time):; CNRS. 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.; Institut Pasteur PTR, Fondation pour l'Audition. **N. Gonçalves:** None. **A. Buck:** None. **C. De Campos Pina:** None. **T. Dupont:** None. **N. Michalski:** None. **L. Arnal:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

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European Union's Horizon 2020 research and innovation programme under grant agreement No 964568, project Hearlight

Title: A spatial code for temporal information is necessary for auditory learning

Authors: *S. BAGUR[1], J. BOURG[1], A. KEMPF[1], T. TARPIN[1], K. BERGAOUI[1], Y. GUO[1], S. CEBALLO[1], J. SCHWENKGRUB[1], A. VERDIER[1], J.-L. PUEL[2], J. BOURIEN[2], B. BATHELLIER[1];
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Abstract: The temporal structure of sensory inputs contains essential information for their interpretation. Sensory cortex represents these temporal cues through two codes: the temporal sequences of neuronal activity and the spatial patterns of neuronal firing rate. However, it is unknown which of these coexisting codes causally drives sensory decisions. To separate their contributions, we generated in the mouse auditory cortex optogenetically-driven activity patterns differing exclusively along their temporal or spatial dimensions. Mice could learn to behaviorally discriminate spatial but not temporal patterns. Moreover, large-scale neuronal recordings across the auditory system indicated that the auditory cortex is the first region in which spatial patterns efficiently represent temporal cues on the time scale of several hundred milliseconds. This feature is shared by the deep layers of neural networks categorising time-varying sounds. Therefore, the emergence of a spatial code for temporal sensory cues is a necessary condition to

associate temporally structured stimuli with decisions. We expect this constraint to be crucial for re-engineering perception by cortical stimulation.

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Poster

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Topic: D.05. Auditory & Vestibular Systems

Support: NIH grant DC009836

Title: Cortical PV neurons shape the neural code for loudness perception and are a critical point of failure in auditory hypersensitivity disorders

Authors: *K. K. CLAYTON[1,2], M. MCGILL[1], B. AWWAD[1,2], K. STECYK[1], D. NARAYANAN[1], C. KREMER[1], Y. WATANABE[1], K. HANCOCK[1], E. KOZIN[1,2], D. B. POLLEY[1,2];
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Abstract: The auditory periphery converts a million-million-fold change in acoustic signal energy (120 dB) into an electrochemical code for sound intensity. The central auditory pathway, in turn, converts this sound intensity code into the perception of loudness. The essential circuitry for intensity-to-loudness transformation has not been identified, though there is reason to believe that dysfunction in these circuits could produce hypersensitivity to sound. Here, we tested the hypothesis that local circuits formed between parvalbumin-expressing (PV) GABA neurons and excitatory (RS) neurons in the mouse primary auditory cortex (A1) mediate loudness perception and are a critical failure point in hyperacusis.
A1 single unit recordings revealed heterogeneous intensity tuning that was aggregated at the level of the cortical column into a linear readout of sound level that could be decoded with high accuracy. Optogenetic inactivation or activation of A1 PV neurons imposed opposite shifts in sound intensity coding towards temporary neural hyperacusis or hypoacusis, respectively (n = 6 mice/177 units). To directly relate PV activity to loudness perception, head-fixed mice were trained in a two-alternative forced choice categorization task. Bilateral optogenetic inactivation or activation of A1 PV neurons immediately and reversibly shifted the perceptual boundary between soft and loud sound reporting, respectively, suggesting that A1 PV neurons function as a volume knob for loudness perception (N=12).
To test whether reduced PV-mediated inhibition is an underlying cause of hyperacusis, we induced hearing loss in the high-frequency base of the cochlea with noise. After cochlear injury,

A1 RS units were hyper-responsive to spared mid-frequency tones and were less suppressed by optogenetic PV activation (N = 6/484 units). Noise-exposed mice also exhibited hyperacusis in loudness categorization compared to sham-exposed controls (N = 10). Importantly, optogenetic activation of PV neurons in hyperacusic mice (N = 5) transiently shifted loudness categorization back to pre-exposure levels.
Finally, we asked if high-frequency stimulation of PV neurons could reinvigorate PV-mediated inhibition and stably reverse hyperacusis. We found that activating PV neurons for 15 minutes at 40 Hz - but not 1Hz - reduced sound-evoked spiking in A1 RS units up to 60 minutes later (N = 13/242 units) and shifted behavioral loudness categorization towards softer sounds for up to 1 week (N = 4). These findings identify new therapeutic targets for hyperacusis, a common sensory component in neurodevelopmental disorders, aging, and sensorineural hearing loss.

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Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.05/CC2

Topic: D.05. Auditory & Vestibular Systems

Title: Cortical subpopulations perform computations to produce noise invariant representations of frequency embedded in noise

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Abstract: Discriminating relevant auditory signals from background noise poses a fundamental challenge to sensory systems. In rodents, the auditory cortex (ACtx) is known to play a key role in disentangling auditory signals from background noise; however, the specific contributions of distinct cortical subpopulations remain elusive. We investigated how subsets of excitatory neurons in ACtx layer (L) 2/3 and 5 process sensory signals in the presence and absence of noise. We focused on intratelencephalic (IT) neurons in L2/3 and both IT and extratelencephalic (ET) neurons in L5, each distinct excitatory subset characterized by distinct functional, synaptic, and anatomical properties. Our objective was to elucidate the functional mechanisms these subpopulations use to disentangle signal from noise. Using genetically modified mouse lines and viral techniques, we conducted *in-vivo* two-photon calcium imaging of L2/3 and L5 (IT and ET) neurons while presenting pure tones varying in frequency and intensity in the presence or absence of broadband white noise (50 dB SPL). At the single neuron level, L2/3 neurons exhibited a prominent reduction in responses relative to their preferred frequency. This reduction was both subtractive and divisive, determined through regression analysis, consistent with previous work. In contrast, L5 IT and ET neurons exhibited similar responses for both

conditions. We analyzed the stimulus information content and complexity of cortical communications through binary decoding and population dimensionality, respectively. Population dimensionality analysis demonstrated that the number of dimensions used by L2/3 and L5 neurons for inter-neuronal communication remained unchanged across the conditions. Furthermore, we observed that the dimensionality of L5 IT-ET neuron communication remained constant regardless of noise conditions, suggesting that disentangling signal from noise does not necessitate increased neural complexity. Finally, we trained a support vector machine to detect the presence of a tone based on neuronal population activity. Despite their differences at the single neuron level, both L2/3 and L5 populations exhibited improved discrimination in absence of noise, with higher d-prime values for similar tone intensities. Our findings suggest that tone responses at the single-neuron and population-level differ when in the presence of noise. Within the cortical column, L2/3 representations of tone in noise likely undergo local computations to disentangle pure tones from white noise. This dissociated information is then transmitted to L5, facilitating its broadcast to relevant cortical and subcortical structures.

Disclosures: T. Suarez Omedas: None. **R.S. Williamson:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

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Program #/Poster #: PSTR275.06/CC3

Topic: D.05. Auditory & Vestibular Systems

Support: U19 900937722

Title: Alteration of behavior using optogenetic manipulation of auditory cortical circuits

Authors: *K. J. MAXIMOV, P. JENDRICHOVSKY, P. O. KANOLD;
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Abstract: Ensembles or small networks of coactive cells in the auditory cortex seem to be the key cortical representations of both stimuli and behavioral choice during auditory detection task performance (Francis et al., 2018). While modeling work suggests that activating one or few “pattern completion” neurons in these small ensembles may be enough to drive the activity of the full ensemble and hence recreate the stimulus representation or behavioral choice artificially (Carillo-Reid et al., 2021; Pancholi et al, 2023), experimental evidence is lacking. Thus, we investigated if small numbers of neurons in the auditory cortex could play a causal role in driving auditory behavior questions by holographic optogenetic stimulation, which allows one to precisely and causally probe the role of specific neurons during behavior. To first explore the parameter space of such stimulation and its effects on an auditory detection behavior task we trained mice on a simple go/no go detection task where the object was to respond to a tone in the presence of varying levels of white noise. We imaged neural activity in primary auditory cortex (A1) using GCaMP7. A1 cells also expressed a red-shifted opsin (e.g. ChroME), allowing for

both imaging and targeted stimulation. After mice reached the training criteria, stimulation was performed during behavioral trials interspersed with non-stimulation trials. Neurons were selected for stimulation either randomly or based on their tuning curves. We find that holographic stimulation can change the activity of targeted cells in A1. We also found that stimulation of small groups of A1 cells can alter tone-detection behavior. Our work suggests that holographic optogenetic stimulation of small groups of cells in A1 during behavior can alter auditory behavior. Thus, small groups of A1 neurons seem to be able to causally influence behavior.

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Poster

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Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R01DC018650
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Title: Role of the cholinergic system in early sensorimotor acquisition

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Abstract: During sensorimotor learning, animals link a sensory cue with actions that are separated in time using circuits distributed throughout the brain. Learning thus requires neural mechanisms that can operate across a wide spatiotemporal scale and promote learning-related plasticity. Neuromodulatory systems, with their broad projections and diverse timescales of activity, meet these criteria and have the potential to link various sensory and motor components. Yet, it remains unknown the extent to which this proposed model of plasticity occurs in real-time during behavioral learning. The acquisition of sensorimotor learning in a go/no-go task has been found to be faster and more stereotyped than previously thought (*Kuchibhotla et al., 2019*). We trained mice to respond to one tone for a water reward (S+) and withhold from responding to another (S-). We interleaved reinforced trials with those where reinforcement was absent ("probe"). Early in learning, animals discriminated between S+ and S- in probe but not

reinforced trials. This unmasked a rapid *acquisition* phase of learning followed by a slower phase for reinforcement, termed '*expression*'. What role does cholinergic neuromodulation play in task acquisition? Here, we test the hypothesis that cholinergic neuromodulation provides a 'teaching signal' that drives primary auditory cortex (A1), and links stimuli with reinforcement. We exploit our behavioral approach and combine this with longitudinal two-photon calcium imaging of cholinergic axons in A1 during discrimination learning. We report both robust stimulus-evoked cholinergic activity to both S+ and S- and stable licking-related activity throughout learning at the level of the axon segment. While this activity mildly habituates in a passive control, in behaving animals the S+ and S- stimulus-evoked activity is enhanced (S+: duration, S-: amplitude and duration) on the timescale of acquisition. Additionally, we test the hypothesis that cholinergic neuromodulation impacts the rate of task acquisition. We expressed ChR2 bilaterally in cholinergic neurons within the basal forebrain of ChAT-cre mice and activated these neurons on both S+ and S- trials throughout learning. Test animals acquired the task faster than control groups. These results suggest that phasic bursts of acetylcholine, projecting widely to cortical regions, directly impact the rate of discrimination learning.

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Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

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Topic: D.05. Auditory & Vestibular Systems

Support: NIH F31 DC020361 to MNS

Title: Visual cues modulate auditory responses in the macaque inferior colliculus

Authors: *M. N. SCHMEHL[1], S. T. TOKDAR[2], J. M. GROH[3];
[1]Neurobio., [2]Statistical Sci., [3]Psychology & Neurosci., Duke Univ., Durham, NC

Abstract: How the brain uses multisensory cues to process complex sensory environments remains a key question in neuroscience. Of particular interest is whether relatively early sensory areas, which are commonly considered to be unisensory in function, might take in information from other sensory modalities to inform the representation of the primary modality of interest (for review, see Schmehl & Groh, *Annual Review of Vision Science* 2021). We explored how visual cues might inform the representation of sounds in the macaque inferior colliculus, a subcortical auditory region that receives visual input and has visual and eye movement-related responses.
We conducted *in vivo* single- and multi-unit extracellular recordings in the inferior colliculus while two monkeys (*Macaca mulatta*, one female age 15 years, one male age 7 years) performed a localization task involving both auditory and visual stimuli. We found that pairing a visual cue

with a sound can change a neuron's response to that sound, even if the neuron is unresponsive to visual input alone. Visual cues also enhance localization behavior in both spatial precision and temporal latency. Finally, when two simultaneous sounds are present and one sound is accompanied by a visual cue, neurons are more likely to respond to the visually-paired sound on individual trials. Together, these results suggest that the inferior colliculus uses visual cues to alter its sound responsiveness and inform perceptual behavior, providing insight into how the brain combines multisensory information into a single perceptual object at a relatively early stage of the auditory pathway.

Disclosures: **M.N. Schmehl:** None. **S.T. Tokdar:** None. **J.M. Groh:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

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Topic: D.05. Auditory & Vestibular Systems

Support: ZIAMH002881

Title: Processing of valence-associated stimuli in the murine auditory cortex

Authors: ***J. JOHNSON**[1], Z. LI[2];
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Abstract: The auditory cortex is recognized as the primary centre for sound processing in the brain; however, recent evidence suggests its involvement in the processing of an array of non-auditory information. The ability to associate stimuli with emotional or motivational valence is crucial for survival, and disruptions in these associations are observed in disorders like PTSD and schizophrenia. While the impact of rewarding or aversive associations on tone frequency processing has been investigated, the neuronal mechanisms underlying the intersection of these factors and the existence of innate or conditional valence responsiveness in the auditory cortex remain unclear. To address this, we employed longitudinal two-photon GCaMP imaging to examine auditory cortex neuronal responses during conditioning, recall, and combination switching of pure tones paired with rewarding or aversive stimuli. Following conditioning, a subset of auditory cortex neurons displayed responses to valence-coded stimuli when presented in both within pairings and in isolation, comprising cells with and without tone responses. These valence-responsive cells predominantly exhibited activity in the presence of solely rewarding or aversive stimuli, but some also demonstrated responses to both valences. Upon switching the initially conditioned pairings, a substantial subset of neurons exhibited a shift in their stimulus response to the emotionally opposing stimuli. This population additionally showed relationships to the stimuli induced behaviour, which was analysed with DeepLabCut. Using optogenetic activation of the valence sensitive population we observed ensembles with heterogenous

response types consisting of mixed valence and tone-responsive cells, suggesting a local mechanism that influences the effect of emotionally linked auditory information within the auditory cortex. These findings shed light on the complex interplay between auditory processing, emotional valence and behaviour in the murine auditory cortex.

Disclosures: J. Johnson: None. **Z. Li:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

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Topic: D.05. Auditory & Vestibular Systems

Support: Canadian Institutes of Health Research

Title: Neural Correlates of Residual Hearing in the Core and Belt Auditory Areas of Early-deaf Subjects

Authors: *Y. MERRIKHI[1], A. KHADIR[2], C. KRUGER[1], S. JAFARI[3], S. G. LOMBER[1]; [1]Physiol., McGill Univ., montreal, QC, Canada; [2]Iran Univ. of Sci. and Technol., Tehran, Iran, Islamic Republic of; [3]Biomed. engineering, Amirkabir Univ., Tehran, Iran, Islamic Republic of

Abstract: The auditory brainstem response (ABR) is a neurophysiological test utilized to assess the electrical activity produced by the auditory nerve and brainstem in response to auditory stimuli. The absence of a measurable ABR response can indicate significant hearing loss but is not sufficient for confirming deafness. Some individuals classified as profoundly deaf may still possess residual hearing or sensation in response to auditory stimuli. The cortical manifestation of this residual hearing is not well understood. To explore the neural basis of residual hearing in the profoundly deaf, we conducted multiple single-unit recordings from four adult cats that were chemically deafened in the first postnatal month. We recorded in primary auditory cortex (A1) and a belt auditory area known as the Dorsal Zone (DZ), in lightly anesthetized cats. We examined the neural responses to acoustic (white noise bursts, 500 ms duration), visual (80 lux, 500 ms duration), and somatosensory (displacement distance of 1 mm, 500 ms duration) cues presented separately or in combination. We collected neural activity, including spiking activity and local field potentials (LFP), from 380 DZ and 330 A1 recording sites from which we isolated 329 DZ and 252 A1 single neurons. No activation was observed in terms of spiking activity or LFP in the early-deaf cats' auditory areas following acoustic stimulus presentation. However, we did find that an acoustic stimulus significantly decreased the visual or somatosensory responses of neuron populations in both A1 and DZ when it was co-presented with a cross-modal stimulus. Additionally, we observed a significant decrease in the amplitude of LFP responses to somatosensory stimuli in both A1 and DZ in frequency ranges higher than 8 Hz (>α band) following the co-presentation of an acoustic stimulus. In the >α frequency bands, when acoustic and visual stimuli were presented simultaneously, the amplitude of LFP responses in A1 showed

a significant reduction. Conversely, the co-presentation of acoustic and visual stimuli resulted in a significant enhancement of the amplitude of LFP responses in DZ sites. Collectively, these findings provide insights into the neural mechanisms associated with preserved auditory function in individuals with hearing loss and contribute to our understanding of the neural correlates of residual hearing.

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Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

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Program #/Poster #: PSTR275.11/CC8

Topic: D.05. Auditory & Vestibular Systems

Title: Encoding of two tone harmonic complexes and sample nonharmonic complexes in the mouse primary auditory cortex.

Authors: *A. DE, R. ARCHAK, S. BANDYOPADHYAY;
Advanced Technol. Develop. Ctr., Indian Inst. of Technol., Kharagpur, India

Abstract: Two tone harmonic complexes (TTHCs) are one of the common syllable types in mouse vocalization in different socio-behavioral contexts like courtship. TTHCs, containing simultaneously presented fundamental frequency (F_0) and its first harmonic ($F_1 = 2F_0$), showed differential encoding from its component tones at a single neuron resolution in the mouse primary auditory cortex (A1), in our previous study. However, whether the presence of a second component at $2F_0$ is necessary for the differential encoding was unexplored. We ask, how the presence of a second component at a frequency F_n, not an integer multiple of F_0, either below or above $2F_0$ (referred to as Low or High nonharmonic complexes, LTTNC and HTTNC respectively) is different from TTHCs in terms of single neuron response properties. We used only a sample of numerous nonharmonic combinations possible, keeping F_n at 0.25, 0.5, 1.25 and 1.75 octaves from F_0. With single unit responses, in general, two-tone nonharmonic complexes (TTNCs) showed similar percentages of units enhanced, suppressed or no-effect categories; i.e. TTNC responses are larger, lower or not different from the maximum of component tones, respectively. Single units response to TTHCs showed higher mean spike rates from that of TTNC when F_0 and F_n of TTNC is within a narrow range from the best fundamental frequency (BF_0) of the F_0. On the other hand, F_n, as a distant component from BF_0 showed relatively lower mean spike rate. But, normalized rate responses of TTHCs were significantly higher than TTNCs in case of units with best fundamental frequency (BF_0), such that BF_0=F_0, while differential effects were observed in a frequency specific manner when considering units with F_0s at different distances from BF_0. In the current study we also collected 2-photon Ca^{+2} imaging based responses of single neurons in A1 superficial layers of mice, chronically using the same set of stimuli. Similar results were obtained, however with different proportions of units in each class

of comparative responses detailed above. Our study thus shows that TTHCs and TTNCs are encoded differently, especially based on the BF_0 of neurons.

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Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.12/CC9

Topic: D.05. Auditory & Vestibular Systems

Support: Fullbright Program
Howard Hughes Medical Institute
Tianqiao and Chrissy Chen Institute
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NIH/NINDS (R01-NS21135)
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NIH/NINDS (U01-NS108916)
NIH/NINDS (U01-NS128612)
NIH/NIMH (P50-MH109429)
NIH/NIMH (R01-MH120194)
Fondazione Neurone
McDonnell Center for Systems Neuroscience

Title: Responses to unexpected sound omissions in human auditory cortex: electrocorticography and stereo-electroencephalography studies

Authors: *H. CHO[1,2], Y. M. FONKEN[3,4], M. ADAMEK[1,2], R. JIMENEZ[3], G. SCHALK[5,6], J. T. WILLIE[1,2], R. T. KNIGHT[3], P. BRUNNER[1,2,7];
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Abstract: Context modulates sensory neural activations enhancing perceptual and behavioral performance and reducing prediction errors. However, the mechanism of when and where these high-level expectations act on sensory processing needs to be clarified. Here, we isolate the effect of expectation absent of any auditory evoked activity by assessing the response to omitted expected sounds. Electrocorticographic (ECoG, six subjects) and stereo-electroencephalographic (SEEG, another six subjects) signals were recorded. Twelve subjects listened to a predictable

sequence of syllables ('La-La-Ba La-La-Ga'), with some third syllables infrequently omitted ('Ba' or 'Ga'). We found high-frequency band activity (HFA, 70-170 Hz), a surrogate measure of neural excitations, in response to omissions, which overlapped with a posterior subset of auditory-active electrodes in the superior temporal gyrus (STG). However, we found no HFA responses to expected omitted sounds in a control experiment with a predictable omission in the syllable sequence ('La-La- '). Furthermore, the HFA omission response at posterior STG (PSTG) consisted of the six ECoG subjects, while we could not observe these HFA responses in SEEG due to the less coverage over the PSTG area. Interestingly, in ECoG data, the time series pattern of HFA in omission shows that the omission HFA response was increased from baseline and sustained until the next syllable stimulus. And then, the sustained HFA response returned to the baseline after the syllable stimulus. This pattern indicates that PSTG areas were anticipating for the expected stimulus. Furthermore, in both ECoG and SEEG, the HFA onsets in PSTG were earlier than other STG areas for both syllable and omission conditions, while in general, the earliest HFA responses are near the primary auditory cortex.The significance of the HFA responses to unexpected omission conditions is that the PSTG location is involved in omission processing and monitoring each expected syllable. Based on our results, we infer that PSTG monitors auditory inputs and anticipates for expected auditory information. We propose that the HFA responses at PSTG are involved in processing context information to enhance perceptual and behavioral performance and reduce prediction errors. HFA omission responses in this region appear to index mismatch-signaling or salience detection processes.

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Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.13/CC10

Topic: D.05. Auditory & Vestibular Systems

Support: CONACYT grant CF-2019-6390

Title: Heritability of auditory cortex’s morphology in the mexican population

Authors: *G. ROBLES RODRÍGUEZ[1,4], D. RAMÍREZ GONZÁLEZ[1], M. GARCÍA GOMAR[2], I. ESPINOSA MÉNDEZ[1,2], I. SANCHÉZ MONCADA[1], T. ROMÁN LÓPEZ[1], X. DÍAZ TÉLLEZ[1,3], C. DOMÍNGUEZ FRAUSTO[1], V. MURILLO LECHUGA[1], X. LÓPEZ CAMAÑO[1], G. GUZMÁN TENORIO[1], O. ALDANA ASSAD[3], A. MEDINA RIVERA[3], A. RUÍZ CONTRERAS[2], M. RENTERÍA[4], S. ALCAUTER SOLÓRZANO[1];
[1]Inst. de Neurobiología., Univ. Nacional Autónoma de México, Querétato, Mexico; [2]Escuela Nacional de Estudios Superiores Juriquilla, [3]Lab. Internacional de Investigación sobre el Genoma Humano, Univ. Nacional Autónoma de México, Querétaro., Mexico; [4]QIMR Berghofer Med. Res. Inst., Brisbane, Australia

Abstract: Heritability of auditory cortex's morphology in the mexican populationThe auditory system consists of multiple brain regions, including the transverse temporal gyrus and the superior temporal gyrus, which contain the primary and secondary auditory cortices, respectively. These two regions are essential for high-order perceptual processes. The morphology of these regions varies across individuals, and these variations might be associated with auditory perceptual and cognitive skills (Turker et al, 2019). Cortical morphology has been shown to be heritable, variations on these phenotypes are partially explained by genetic factors. Heritability can be estimated by measuring the correlation of a quantitative trait in monozygotic twins (MZ) - who share around 100% of their DNA - against the correlation within dizygotic twins (DZ) - who share 50% of their DNA, on average. However, heritability could differ across populations. Most research on heritability has been conducted on people of European ancestry, while Latin Americans remain underrepresented. The objective of this study is to estimate the heritability of the auditory cortex's morphology. We acquired high-resolution T1w images in 214 twins (138 MZ and 76 DZ) from the Mexican Twin Registry (TwinsMX). These were preprocessed and parcellated using FreeSurfer's recon-all pipeline. Two brain regions within the temporal lobe were selected for analysis: transverse temporal gyrus, and superior temporal gyrus. We estimated the heritability of their cortical thickness and surface area for both hemispheres. For cortical thickness, we found a higher correlation among identical twins for the right (rMZ=.42, rDZ= .40), and left (rMZ=.57, rDZ=.41) transverse temporal gyrus, and for the right (rMZ=.67, rDZ=.56), and left (rMZ=.64, rDZ=.50) superior temporal gyrus. For surface area, we also found a higher correlation among identical twins for the right (rMZ=.57, rDZ=.40), and left (rMZ=.72, rDZ=.08) transverse temporal gyrus, and for the right (rMZ=.76, rDZ=.59), and left (rMZ=.77, rDZ=.70) superior temporal gyrus. These results suggest that variations in the morphology of the auditory cortex is partially explained by genetics.
References Turker, S., Reiterer, S. M., Schneider, P., & Seither-Preisler, A. (2019). Auditory cortex morphology predicts language learning potential in children and teenagers. *Frontiers in neuroscience*, *13*, 824.

Disclosures: G. Robles Rodríguez: None. **D. Ramírez González:** None. **M. García Gomar:** None. **I. Espinosa Méndez:** None. **I. Sanchéz Moncada:** None. **T. Román López:** None. **X. Díaz Téllez:** None. **C. Domínguez Frausto:** None. **V. Murillo Lechuga:** None. **X. López Camaño:** None. **G. Guzmán Tenorio:** None. **O. Aldana Assad:** None. **A. Medina Rivera:** None. **A. Ruíz Contreras:** None. **M. Rentería:** None. **S. Alcauter Solórzano:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.14/CC11

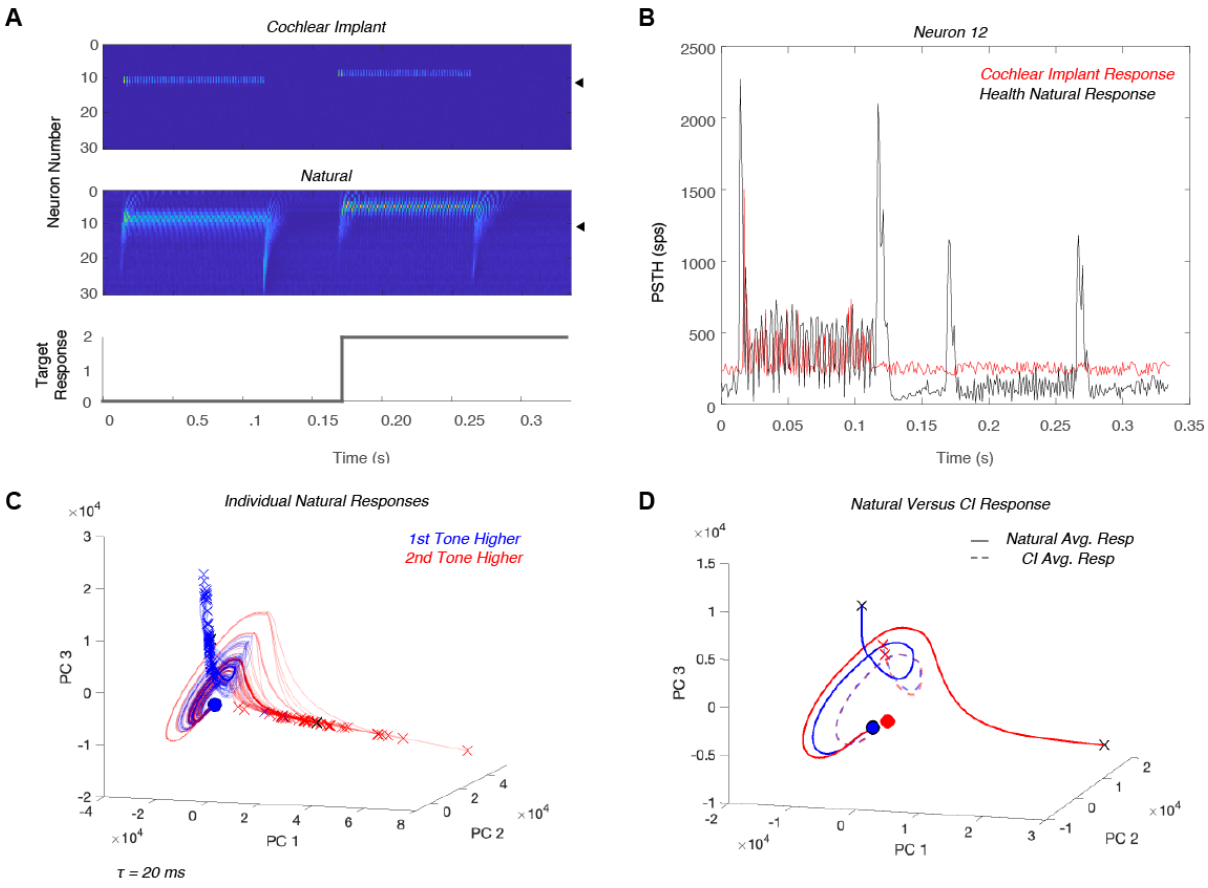
Topic: D.05. Auditory & Vestibular Systems

Support: Simons Society of Fellows Junior Fellowship

Title: Identifying Features of Cochlear Implant Stimulation that Obstruct Tone Discrimination at the Network Processing Level

Authors: *C. STEINHARDT;
Columbia Univ., New York, NY

Abstract: Cochlear implants(CIs) are arguably the most successful neural implant in clinical use. They use sparse electrical encoding and simple pulsatile stimulation patterns but provide patients with enough information to perform speech recognition. Still, they have deficits such as poor restoration of tone information. Here, we investigate how tone discrimination capabilities are lost during auditory stream processing by analyzing how CI stimulation affects a recurrent neural network trained to perform tone discrimination to naturalistic cochlear fiber responses. "Natural" responses were simulated as a combination of low, medium and high spontaneous rate fiber response at 30 locations along the cochlear with different characteristic frequencies. A CI response to the same stimulus was created by simulating the location of Cochlea Nucleus-22 electrodes in the cochlea and using the Cochlear NMT Toolbox to simulate the transformation of sound into stimulation per electrode site. Gaussian current spread up to 1 mm from the electrode was assumed to determine the spiking per fiber. Thus, a natural or CI-induced cochlear response could be generated to any input. The tone task was determining whether the first or second tone in a sequence is higher. Tones were varied from 0.5 to 10 semitones above a base tone within frequencies less than 20,000 Hz. This produced a 1200 cases dataset that was split into a training and test set. Cross entropy loss was used to train the network. The network performed the task with 100% accuracy using natural inputs and at a chance level in using CI inputs on the test set. This performance indicates that tone information was lost when CI stimulation drove the network. Principal component analysis revealed that the network separates the two cases in representation space for naturalistic inputs. CI stimulation drives neural activity similarly for both cases into a network attractor. Using this model, we will investigate what aspects of CI stimulation cause this misrepresentation of tones and how the paradigm could be altered to restore tone encoding to a closer to natural level.



Disclosures: C. Steinhardt: None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.15/CC12

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant 5R01DC018055-05

Title: Relational invariance through combinatorial population spiking

Authors: *T. S. MCPHERSON, B. H. THIELMAN, T. GENTNER;
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Abstract: Relational invariance—a network's ability to capture the geometric relationships between external inputs abstracted away from explicit variables—provides a potential

mechanism for robustness and generalizability in neural networks. Previous work from our group demonstrates relational invariance empirically, revealing a combinatorial spiking code that captures the relational geometry of acoustic stimuli in the songbird brain. To understand how relational invariance might emerge through combinatorial population spiking, we develop a spiking neural network (SNN) modeling framework that captures the relationships between different patterns of input signals. We train SNNs to autoencode continuous input streams via unsupervised, local, and biologically inspired learning rules. Using a probabilistic population model constructed from the receptive fields of individual SNN neurons, we show that the combinatorial population responses in the trained SNN intrinsically capture the relational geometry between input signals, demonstrating relational invariance in the SNN. This structure can be observed without the use of receptive-field models for inference, which assume a specific parameterization of the external inputs. We go on to explore how relational invariance emerges from this combinatorial code: (1) In the SNN, neural excitability and membrane voltage encode representational error, and we demonstrate the mechanism through which increased firing rates produce greater representational precision. (2) Excitation-inhibition balance is critical for the efficient representation of information, and we show that inhibition dominated networks produce a convex representational geometry through lateral inhibition between similarly tuned neurons. (3) We illustrate how relational invariance is a natural consequence of the network's convex representational geometry. The work demonstrates a novel combinatorial encoding framework through which relationships between any set of external variables can be captured in precise spike-timing dynamics. We suggest that similar coding schemes may be observed in both biological and artificial SNNs.

Disclosures: **T.S. McPherson:** None. **B.H. Thielman:** None. **T. Gentner:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.16/CC13

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant R01EB028155
NIH Grant R01DC014950

Title: Tools for neural network analysis of biological sound processing

Authors: J. R. PENNINGTON[1], ***S. V. DAVID**[2];
[1]Washington State Univ., Vancouver, WA; [2]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Encoding models for the auditory system, such as the spectro-temporal receptive field (STRF) and related linear-nonlinear (LN) models, have proven valuable for understanding the auditory periphery. However, these tools are unable to account for high-order, invariant representations in more central brain areas, including auditory cortex. Numerous alternatives

have been proposed that improve on LN models, but the complexity of model fitting and evaluation has made it difficult to compare their performance directly. We have developed the Neural Encoding Model System (NEMS), an open-source Python library that implements a wide range of encoding models for analysis of auditory neural data. NEMS has a building-block design that permits a continuum of simple (LN) to complex (convolutional neural network, CNN) models. Models can use standard LN units or incorporate biological nonlinearities, such as short-term synaptic plasticity. They can also incorporate state variables that account for non-auditory context that modulates auditory processing. Different models can be fit and evaluated using cross validation and applied to fixed datasets, allowing unbiased comparison of alternative model architectures. One additional challenge to developing models of central auditory processing is understanding the functional properties captured in their complex non-linear transformations. To address this issue, we have incorporated the dynamic STRF tool into NEMS, which permits visualizing locally linear, LN approximations of a model under different stimulus conditions and contexts. Our current studies show that CNN-based models provide substantially greater predictive power than any other model tested.

Disclosures: **J.R. Pennington:** None. **S.V. David:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.17

Topic: D.05. Auditory & Vestibular Systems

Support: BBSRC New Investigator Award (BB/M010929/1)

Title: Single neuron and population codes for pitch in auditory cortex

Authors: *K. M. M. WALKER[1], V. TARKA[2], Q. GAUCHER[3];
[1]Physiology, Anat. & Genet., Univ. of Oxford, Oxford, United Kingdom; [2]Oxford Univ., Oxford, United Kingdom; [3]ENS, Paris, France

Abstract: Harmonic sounds in our natural environments almost always contain energy at a collection of frequencies. However, we experience these sounds as having a unitary tonal quality at a fundamental frequency, known as its pitch. Pitch perception plays a key role in our experience of speech and music, as well as our ability to segregate multiple sound sources. While some studies in marmosets and humans have suggested that pitch may be processed by a highly specialized subpopulation of neurons in auditory cortex, the evidence across animal models remains inconclusive and heavily debated. I will discuss our modelling, electrophysiological, and behavioural experiments in ferrets, which offer insights into how single neurons and populations of neurons in auditory cortex encode the pitch of sound. We show that different classes neurons can extract pitch from either the temporal periodicity of the soundwave in time, or the harmonicity of the sound in the frequency domain. I will discuss the extent to which well-known

tonotopic maps of sound frequency in the brain may contribute to pitch processing, and the open question of whether auditory cortex may contain a specialized pitch processing centre.

Disclosures: K.M.M. Walker: None. **V. Tarka:** None. **Q. Gaucher:** None.

Poster

PSTR275. Auditory Processing: Neural Coding, Experiment, and Theory

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.18/CC14

Topic: D.05. Auditory & Vestibular Systems

Support: H2020 ERC Consolidator Deepen
Fondation pour l'Audition, IdA Starting grant 002

Title: Towards two-photon all-optical electrophysiology with acousto-optic scanning

Authors: *M. PISONI[1], B. MATHIEU[2], P. BIZOUARD[3], S. DIEUDONNÉ[2], B. BATHELLIER[1];
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Abstract: Precise and efficient investigation of neuronal circuits underlying sensory perception remains to date one of the biggest technical challenges in neuroscience, despite the tremendous advancements integrated over the fields of molecular biology, engineering, optics, and computer science during the last two decades. Currently, two-photon (2P) microscopy is considered the state-of-the-art technique to record and simultaneously perturb the activity of large population of neurons, using an all-optical strategy. 2P functional imaging grants high (single cell) spatial resolution, with temporal resolution compatible with the most recent genetically encoded calcium sensors. When dissecting a neuronal circuit of interest, though, it would be ideal to directly access and manipulate the sub- and supra-threshold electrical activity of neurons. Recently, several genetically encoded voltage indicators have been developed, along with imaging strategies suitable for recording electrical signals (kilo-hertz range), without compromising spatial resolution. Among these, ULoVE (Villette et al. 2019) is an ultrafast high signal-to-noise ratio imaging technique, already validated for 2P voltage imaging *in vivo* (Villette et al. 2019; Liu et al. 2022). In this framework, similarly accurate 2P optogenetic perturbation is lacking. For this reason, we tested the possibility of using the same approach (ULoVE) to perform ultrafast excitation of multiple neurons. Employing low repetition rate femtosecond lasers, coupled with an AOD-based microscope, it was possible to perform exquisitely spatially and temporally precise photostimulation of ensembles of neurons *in vivo*. As a proof of principle, neurons co-expressing the calcium indicator GCaMP6m and the large conductance excitatory opsin ChRmine (Marshel et al. 2019) where simultaneously imaged and

briefly (< 150µs) photostimulated, resulting in successfully evoked fluorescent transients. These results demonstrate the feasibility of stimulating neuronal ensembles with unprecedented temporal resolution, matching kinetics and latency of physiological electricals signals. In this framework, we performed chronic voltage imaging using the most recent genetically encoded voltage indicator JEDI-2P (Liu et al. 2022) to monitor the electrical activity of L2/3 pyramidal neurons in mouse auditory cortex. In future experiments, we plan to perform all-optical electrophysiology experiments to investigate the role of specific ensembles of auditory cortex neurons in processing sounds information.

Disclosures: **M. Pisoni:** None. **B. Mathieu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Karthala System, 91400 Orsay, France. **P. Bizouard:** A. Employment/Salary (full or part-time):; Karthala System, 91400 Orsay, France. **S. Dieudonné:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Karthala System, 91400 Orsay, France. **B. Bathellier:** None.

Poster

PSTR276. Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.01/CC15

Topic: D.05. Auditory & Vestibular Systems

Support: Internal grant from the Donders Centre for Cognition

Title: Context-dependent priors in vestibular distance estimation

Authors: *S. C. M. J. WILLEMSEN[1], L. OOSTWOUD WIJDENES[1], R. J. VAN BEERS[1,2], M. KOPPEN[1], W. P. MEDENDORP[1];
[1]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands; [2]Dept. of Human Movement Sci., Vrije Univ., Amsterdam, Netherlands

Abstract: Perception and action depend on our sensory inputs as well as prior experience. How we combine these types of information is often studied with Bayesian models representing sensory and prior information as probability distributions. It has been suggested that the prior corresponds to the sensory statistics during natural activities. For example, we previously found that the distribution of vestibular input measured outside the lab was non-Gaussian. Yet, data from lab-based vestibular perception tasks are better explained using a Gaussian prior distribution. This raises the question whether people build up context-dependent priors for vestibular perception. To this end, we designed a vestibular distance reproduction task in the dark. Participants were first passively moved some distance using a linear motion platform, after which they actively reproduced this distance by moving the platform with a steering wheel. Distances were either sampled from a 'short' or 'long' distance distribution. We introduced two experimental conditions in which the same distances were presented but in different contexts:

short and long distances were either interleaved or presented in two separate blocks. Preliminary results indicate that participants made active movements that were generally shorter than the passive ones. Furthermore, the contexts in which the distances were presented influenced the reproduction behavior. In the blocked condition, the short distances led to shorter reproduced distances than in the interleaved condition and similarly, the long distances resulted in longer reproduced distances, possibly pointing to the presence of context-dependent priors built up during the experiment.

Disclosures: S.C.M.J. Willemsen: None. **L. Oostwoud Wijdenes:** None. **R.J. Van Beers:** None. **M. Koppen:** None. **W.P. Medendorp:** None.

Poster

PSTR276. Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.02/CC16

Topic: D.05. Auditory & Vestibular Systems

Support: NSERC RGPIN-2922-04402
FRQS 329974
CFI 41889

Title: Dance training alters eye-head coordination

Authors: *K. MOÏN-DARBARI[1,2,3], M. NOORISTANI[4], B.-A. BACON[5], F. CHAMPOUX[1,3], M. MAHEU[6,2];
[1]Univ. de Montréal, Montreal, QC, Canada; [2]Ctr. for Interdisciplinary Res. in Rehabil. of Greater Montreal, Montreal, QC, Canada; [3]Res. Ctr. of the Univ. Inst. of Geriatrics of Montreal, Montreal, QC, Canada; [4]Univ. d'Ottawa, Ottawa, ON, Canada; [5]Carleton Univ., Ottawa, ON, Canada; [6]Univ. de Montéal, Montreal, QC, Canada

Abstract: Long-term dance training is known to improve postural control, especially in challenging postural tasks. However, the effect of dance training on the vestibulo-ocular reflex (VOR) has yet to be properly assessed. This study directly investigated whether VOR parameters are influenced by long-term dance training by testing dancers and controls using the video head impulse test. VOR gains using two of the most common methods (area ratio and instantaneous gains), latency and amplitude of the first saccade, if applicable, were computed. Results revealed a larger VOR gain as measured by area gain and by instantaneous gain at 40ms specifically for left head impulses, but not for right head impulses. No significant differences in saccade frequency, amplitude or latency were observed between groups. These differences appear to stem from a modified eye to head relationship during high velocity head impulses in dancers. More specifically, the dancers' eyes lead head movement during passively applied head impulses, which result in higher VOR gain. This finding is discussed in line with the active inference theory based on the free-energy principle.

Disclosures: **K. Moïn-Darbari:** None. **M. Nooristani:** None. **B. Bacon:** None. **F. Champoux:** None. **M. Maheu:** None.

Poster

PSTR276. Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.03/CC17

Topic: D.05. Auditory & Vestibular Systems

Support: CNRS
FRM DEQ20170336764
ANR-22- CE16-0004-02
ANR-22-CE37-0002-02

Title: Developmental switch in vestibulo-spinal neuronal phenotypes during the Xenopus metamorphosis

Authors: *F. M. LAMBERT[1], G. BARRIOS[1], T. FEVRIER[1], A. OLECHOWSKI-BESSAGUET[1], L. CARDOIT[1], M. THOBY BRISSON[2];
[1]INCIA CNRS UMR5287 Univ. of Bordeaux, Bordeaux, France; [2]Univ. De Bordeaux, CNRS UMR 5287, Univ. De Bordeaux, CNRS UMR 5287, Bordeaux Cedex, France

Abstract: Vestibular neurons involved in vestibular pathways exhibit distinct intrinsic membrane properties tuned to ensure various sensory-motor tasks. The frog metamorphosis represents a relevant neuronal plasticity model to investigate this neural computation. In adult frog, vestibular neurons present 2 phenotypes according to their discharge dynamic: 1) Phasic neurons exhibiting a high-frequency burst of 1-3 spikes, without subsequent continuous discharge, due to the ID conductance mainly supported by the Kv1.1 K+ channel and 2) tonic neurons firing continuously. However, such a characterization remains unrelated to a specific vestibular function and nothing is known about the maturation of these neuronal dynamics. This study aims to investigate the maturation of membrane properties specifically expressed in vestibulospinal (VS) neurons involved in postural control, during the re-modeling of the body induced by the metamorphosis in Xenopus. On brainstem slice preparations, patch-clamp recordings of retrogradely labeled VS neurons revealed a reverse proportion between tonic and phasic neurons from larva (20% of phasic) to juvenile (70% of phasic) whereas electrophysiological properties for both phenotypes did not change significantly during this period. Concomitantly Kv1.1 immuno-labeling also revealed a reverse proportion of Kv1.1+ VS neurons from larva (25% of Kv1.1+) to juvenile (65% of Kv1.1+). The highest proportion of Kv1.1+ VS neurons was even reached at the climax (stage 60: Kv1.1+ VS neurons = 77%), demonstrating that the switch occurred at the pro-metamorphosis (stage 54-58).BrDU PULSE-CHASE showed that none of VS neurons present in juvenile originated from mitotic cells older than larval stage 50 and only 15% from stage 50, suggesting that 85% of juvenile VS neurons originated from early larval period. Half of the 15% juvenile VS neurons originating from

mitotic cells at stage 50 were Kv1.1+ which represented only 11% of the total population of juvenile VS Kv1.1+ neurons, presumably exhibiting a phasic phenotype.Altogether these results revealed a developmental switch in the expression of neuronal phenotypes dedicated to vestibulospinal pathways and demonstrated that all VS neurons come from pre-mitotic progenitors established in early larval life. These progenitors could constitute a stock of post-mitotic neuroblasts until stage 50 when enter in their final neuronal differentiation phase (to become either phasic or tonic) when the metamorphosis starts, around stage 54.

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Poster

PSTR276. Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.04/CC18

Topic: D.05. Auditory & Vestibular Systems

Support: faculty grant of Yonsei University College of Medicine (6-2018-0107)

Title: Complexity in discerning the effect of virtual reality immersion using simulator-sickness questionnaire (SSQ)

Authors: *E. SON, S. SHIN, Y. KO, S. LEE;
Dept. of Otorhinolaryngology, Yonsei Univ. Col. of Med., Yongin, Korea, Republic of

Abstract: Virtual reality (VR) technology can provide virtual environments tailored to match the specific needs of patients with dizziness for vestibular rehabilitation. The simulator-sickness questionnaire (SSQ) is widely used to assess the user's discomfort for newly developed VR programs. Since SSQ was originally developed for flight simulators, it remains to be determined whether the SSQ is adequate to measure the severity of subjective symptoms due to VR immersion. We have developed VR-based programs for customized vestibular rehabilitation to evoke subjective perception of motion. Twenty healthy volunteers and 10 patients with chronic dizziness performed VR programs, and SSQ and vertigo-VAS were measured after VR immersion. All subjects were exposed to VR environment, with >90 deg vertical and >180deg horizontal field of view using projected on virtual visual surround. Exploratory factor analysis for two was performed on 16 items of the SSQ, and the results supported the two factor structure ("nausea" and " oculomotor"). Items 1and 10 were loaded similarly to both factors. While the SSQ is widely applied for VR programs, some individual items might be related to increased stress during trials, rather than the direct effects of VR immersion. Further studies are needed to examine contribution of possible confounding factors including emotional stress and anxiety in SSQ surveys for VR immersion.

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Poster

PSTR276. Vestibular Processing and Perception

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Program #/Poster #: PSTR276.05/CC19

Topic: D.05. Auditory & Vestibular Systems

Support: 1IO1RX001986-01
W81XWH-17-1-0172

Title: Irregular fiber subpopulation distribution in central vestibular neurons

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Abstract: The peripheral vestibular end-organs are innervated by regular and irregular afferent fibers which slowly and rapidly adapt to stimuli, respectively. Due to the physiological and sound-sensitive properties of the irregular fibers (calyx-only neurons), they are more susceptible to noise-induced trauma. Calyx-only terminal projections to the vestibular nuclear complex (VNC) have been shown to produce the calcium buffering protein, calretinin. Subsets of these irregular fibers may be present, which has not been previously shown. This gap in knowledge may be addressed by identifying colocalization of calretinin with vesicular glutamate transporters 1 and 2 (vGluT1 and vGluT2) in the VNC. vGluT has been previously used to define subsets of excitatory neurons. The present study focused on identifying subsets of calyx-only terminals in the VNC using calretinin and vGluTs without the induction of vestibular trauma. Following transcardial perfusion, Sprague-Dawley rat brains were collected, post-fixed, and serial sectioned. Immunohistochemistry was performed for calretinin, vGluT1, and vGluT2 on rostral and caudal VNC sections. Calretinin, vGluT1, vGluT2, colocalized calretinin/vGluT1, and colocalized calretinin/vGluT2 punctate were observed in VNC nuclei to evaluate irregular fiber subpopulations. Our findings demonstrate that calretinin positive terminals may colocalize with vGluT1 or vGluT2. These colocalized terminals were differentially observed throughout VNC subdivisions and in rostral and caudal VNC sections. Additionally, vGluT positive terminals that do not colocalize with calretinin were found throughout the VNC. All calretinin positive terminals did not label for vGluT. Our data indicate subpopulations of irregular afferent fiber projections to the VNC without vestibular injury. These subpopulations may have different functional properties, such as firing rate, which may be attributed to which vGluT is being utilized. Furthermore, differential patterns of colocalization among VNC subdivisions may stem from incoming peripheral end-organ projections. Future studies may evaluate changes in irregular fiber distribution in the VNC following vestibular injury, such as noise-induced trauma. Also, these irregular fiber subpopulations may have differential effects on descending vestibular pathways, therefore, affecting movement and posture.

Disclosures: D. Naqvi: None. **S. King:** None. **R. Braun:** None. **A. Holt:** None.

Poster

PSTR276. Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.06/CC20

Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant F31-DC020390
NIH Grant R01-DC002390

Title: Influence of roll and pitch perturbation dynamics on postural responses in nonhuman primates

Authors: *O. M. E. LEAVITT[1], B. A. RAMADAN[2], K. E. CULLEN[3];
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Abstract: Dynamic balance requires rapid and precise integration of vestibular, somatosensory, and visual inputs. While extensive research has been devoted to understanding human postural responses, questions still remain about the underlying neural control of these responses. To this end, it is essential to characterize normal postural responses in an animal model that allows for direct probing of the neural circuitry driving these responses—in this case, the rhesus monkey. Accordingly, here we investigated postural responses in rhesus monkeys, focusing on roll and pitch perturbations. Two monkeys were trained to perch in a natural position on a force plate in a chamber mounted to a dynamic hexapod motion platform. A head-mounted wireless IMU was used to measure head velocity and acceleration. Head orientation was tracked via a reflective optical tracker, while joint kinematics were estimated from video with DeepLabCut. All perturbations had a total displacement of 10 degrees. Two sets of perturbations were delivered in 2 directions for each rotational axis: one with ‘varying velocity’ (20, 40, 60 deg/s at 500 deg/s^2), and one with ‘varying acceleration’ (200, 500, 1000 deg/s^2 at 40 deg/s).
In response to roll perturbations, monkeys were able to maintain head stability in space throughout the platform motion, so that after the platform stopped the head remained earth-vertical. Responses were symmetrical for leftward and rightward perturbations. Notably, these responses strongly resembled responses to roll perturbations reported in prior studies of human and cat posture. We further found that as velocity increased, the peak roll velocity of the head increased slightly, and the peak torque generated by ground reaction forces showed a similar slight increase. In contrast, the changes in head motion and torque were much larger for platform acceleration.
In contrast, in response to pitch rotations, the monkey’s head motion followed platform motion more closely than for roll. Additionally, due to the asymmetry in the body plan of the animal, the responses to forward vs. backward pitch perturbations were asymmetrical. Interestingly, this led to much larger changes in peak head velocity and peak torque with increasing platform velocity. Finally, we observed increases in both head motion and torque responses with increasing platform acceleration as seen in roll.

These results suggest that rhesus macaque postural responses to support surface tilts depend on the angular acceleration of the platform and provide a platform for studies of the neural control of postural responses.

Disclosures: O.M.E. Leavitt: None. **B.A. Ramadan:** None. **K.E. Cullen:** None.

Poster

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Topic: D.05. Auditory & Vestibular Systems

Support: NIH NIDCD R01-DC002390

Title: Native and prosthetic vestibular contributions to postural responses in nonhuman primates

Authors: *B. A. RAMADAN[1], O. M. E. LEAVITT[1], K. E. CULLEN[2];
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Abstract: Clinical trials of vestibular prostheses have shown significant improvements in postural control and quality of life outcomes, but only mild restoration of vestibulo-ocular reflexes. To date, the stimulation mappings employed in these trials have not considered the natural dynamics of vestibular afferent firing patterns, leaving open questions around optimal prosthetic design. In this study, we initially characterized postural control following complete vestibular loss and then examined the ability to restore function using vestibular prosthesis in a rhesus macaque model.
First, we quantified postural responses following bilateral vestibular loss (BVL) in roll and tilt axes. Head movement and orientation were measured using an IMU and optical tracker, ground reaction forces via a force plate, and joint kinematics were estimated from video (DeepLabCut). Two sets of tilts were applied in pitch and roll axes, varying velocity (20, 40, 60 deg/s at 500 deg/s^2) and acceleration (200, 500, 1000 deg/s^2 at 40 deg/s). Overall, BVL resulted in impaired postural responses. Roll tilts resulted in reversed postural responses, while pitch responses were hypermetric to normal. Limb torque analysis during anterior-directed pitch tilts show compensatory behaviors, indicating the relevance of body plan to asymmetry in pitch tilt response. Roll responses align with the functional capacity demonstrated in humans with BVL.
Next, to assess our ability to restore postural control via prosthetic stimulation, we administered stimulation using both static and naturalistic mappings during repeated tilt perturbations with the same kinematics (40 deg/s at 500 deg/s^2). All tested prosthesis stimulation mappings led to improvements in postural responses within 20 tilts. Interestingly, the most significant enhancement in performance resulted from stimulation mappings that mimicked irregular vestibular afferents, closely associated with postural control. We confirmed the efficacy of the prosthesis by interspersing non-stimulation catch trials throughout the experiment. Catch trial responses more closely resembled pre-stimulation conditions, demonstrating that the vestibular

prosthesis stimulation was responsible for the improvement in postural responses.
In summary, our study demonstrates postural control deficits in monkeys with BVL, while suggesting deficit recovery through biomimetic stimulation using a vestibular prosthesis. These findings enhance our understanding of the vestibular system's role in postural control and provide key insights for developing targeted interventions to return independence to individuals with vestibular loss.

Disclosures: B.A. Ramadan: None. **O.M.E. Leavitt:** None. **K.E. Cullen:** None.

Poster

PSTR276. Vestibular Processing and Perception

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Program #/Poster #: PSTR276.08/DD2

Topic: D.05. Auditory & Vestibular Systems

Support: NIH NIDCD R01-DC018061

Title: The vestibular cerebellum performs computations to generate appropriate motor output to postural muscles for stability

Authors: *R. L. MILDREN, C. BAO, K. E. CULLEN;
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Abstract: The brain integrates sensory information to generate motor output to maintain posture and balance while we are in motion. In particular, the vestibular cerebellum performs essential computations to estimate the motion of our head and body as well as our spatial orientation relative to gravity. This self-motion and orientation information is essential for controlling vestibulospinal reflexes to stabilize head and body posture during unexpected self-motion. However, it is unknown how the integration of vestibular and other self-motion cues by the vestibular cerebellum specifically shapes motor unit activity in postural muscles during everyday activities. Accordingly, the overall aim of this study is to link neuronal activity in the vestibular cerebellum with the behavioural output by simultaneously stimulating and recording from the cerebellar cortex and neck motor units.
First, to characterize cerebellar responses to self-motion, we applied whole body (vestibular stimulation), body-under-head (proprioceptive stimulation), and head-on-body (combined stimulation) linear translations while recording from cerebellar Purkinje cells and neck motor units in alert rhesus monkeys. We used 128-channel silicon read-write probes (Neuropixels) to record and stimulate in the cerebellum, and 40-channel thin-film electrodes to record motor units across the width of splenius capitis. Results showed both Purkinje cell and neck motor unit activity was modulated by vestibular, proprioceptive, and combined stimulation. Furthermore, we observed significant coherence between Purkinje cell spikes and motor units at low frequencies (~2 Hz), and spike-trigger average responses in motor units following Purkinje cell spikes. Next, to causally probe how activating Purkinje cells influences motor output, we applied

electrical microstimulation to Purkinje cells identified on channels of the read-write probe using current steering and observed stimulation-evoked excitatory responses in neck motor units. Taken together, our targeted experimental approach provides the ability to probe the involvement of specific cerebellar regions in the control of postural muscle activity. This approach will shed light on the mechanisms behind the coordination of movement and balance during self-motion in our everyday lives.

Disclosures: R.L. Mildren: None. **C. Bao:** None. **K.E. Cullen:** None.

Poster

PSTR276. Vestibular Processing and Perception

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Program #/Poster #: PSTR276.09/DD3

Topic: D.05. Auditory & Vestibular Systems

Support: UF1NS111695

Title: Loss of alpha 9/alpha 10 nicotinic acetylcholine receptor subunit results in postural deficits in mice

Authors: *T. NIEBUR[1], K. E. CULLEN[2];
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Abstract: The vestibular system is essential for ensuring the maintenance of posture and balance in daily life. The information transmitted via vestibular afferents in the VIII nerve to central pathways has been well characterized. However, the VIII nerve also contains efferent fibers projecting from the brain back out to the vestibular organs. To date, the functional role of the vestibular efferent system in mammals is not understood. One hypothesis is that the mammalian efferent vestibular system is responsible for the calibration of central vestibular pathways during development.Acetylcholine (Ach) is the primary transmitter of the mammalian efferent vestibular system. Ach binds to nicotinic Ach receptors on vestibular hair cells and afferent terminals, which are composed of functional alpha (α)9 and α10 (α9/α10) subunits. In vitro studies show that these subunits mediate efferent activation of the vestibular periphery. Here to understand the role of the efferent vestibular system in intact alert animals we characterized the vestibular function in mice lacking α9/α10 subunits. Three types of tests were performed: i) standard vestibular tests, ii) quantification of the vestibular ocular reflex (VOR), and iii) quantification of movement kinematics during challenging self-motion tasks. We first found no difference between α9-/α10- and control mice performance during standard testing, which included contact and air righting. Second, quantification of VOR was performed by measuring eye movements via video during whole-body sinusoidal rotations (0.2-3 Hz, 16 deg/s). Again, no significant difference was found between α9-/α10- and control mice; The gain and phase of the evoked VOR responses were comparable for both groups during whole-body sinusoidal

rotations. Likewise, no differences were observed in optokinetic response evoked by comparable rotation of the visual surround or quick phase eye movement dynamics. Finally, 6D head movement kinematics were quantified during challenging active self-motion tasks including balance beam and swim testing. Balance beam testing revealed that α9-/α10- mice demonstrated significantly lower power head dynamics than control mice, particularly at higher (> 5 Hz) frequencies. These differences were even more pronounced during the swim test, where significant differences are found across a wide range of frequencies and axes. Taken together, these results indicate that the loss of α9/α10 nicotinic acetylcholine receptors primarily impairs postural stability in mice, further implicating the role of the mammalian efferent vestibular system in maintaining posture and balance.

Disclosures: **T. Niebur:** None. **K.E. Cullen:** None.

Poster

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Program #/Poster #: PSTR276.10/DD4

Topic: D.05. Auditory & Vestibular Systems

Support: Shanghai Municipal Science and Technology Major Project

Title: Exploring self-motion perception in the macaque brain using functional ultrasound imaging

Authors: ***B. LIU**, Y. GU;
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Abstract: Path integration is a key strategy for organisms to perform spatial exploration activities, in which self-motion cues play an important role. Research on self-motion has made significant progress over the last two decades, particularly in studies of primates using functional magnetic resonance imaging (fMRI) and electrophysiological techniques. These studies show that certain brain regions such as 3a, 2v, PIVC, FEF, MSTd, VIP, 7a, VPS, and PCC strongly encode either vestibular or visual self-motion information in humans and macaques . However, due to the limitations of fMRI, experiments have only been able to use galvanic vestibular stimulation (GVS) or caloric vestibular stimulation (CVS) to simulate self-motion. In addition, studies in macaques using electrophysiological techniques do not allow for large-scale, rapid recordings, and only focus on few brain regions at a time. Functional ultrasound imaging (fUSI) has developed rapidly in recent years and has the advantage of high spatial and temporal resolution, a wide recording range, and good compatibility, which could help us to study multiple brain areas simultaneously during realistic self-motion. We have improved and refined this technique to enable long-term stable imaging of the macaque brain with motion. In combination with a virtual reality system, macaques were provided with real motion stimuli in different directions of translation and rotation in 3D space by a motion platform and simulated

visual motion stimuli by optic flow. We have systematically investigated the whole-brain network of self-motion information using the fUSI technique. Based on the correlation between ultrasound Doppler signals and motion stimuli, we screened out candidate brain regions that encode self-motion cues. Not only did we find that the classical brain regions reported previously show vestibular or visual responses, but we also clarified the encoding of different subregions of certain brain regions and found that Brodmann areas 1-2 and 5 encode both vestibular and visual signals, and that 3a and 2v, typical vestibular areas, also carry visual signals. Building on previous work in this area, our study not only improved the fUSI technique which has only been applied to stationary monkeys, but also helped fill a gap in the field by constructing a whole-brain network for vestibular and visual self-motion encoding, opening up new directions for future studies.

Disclosures: B. Liu: None. **Y. Gu:** None.

Poster

PSTR276. Vestibular Processing and Perception

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Topic: D.05. Auditory & Vestibular Systems

Support: JSPS KAKENHI No. 20K19305
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Otemon Gakuin University

Title: A role of right middle occipital gyrus in egocentric spatial orientation when the body is tilted: Evidence from a pre-registered rTMS study

Authors: *K. TANI[1], E. NAITO[2], K. MIZOBE[1], S. HIROSE[1];
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Abstract: Awareness of the relative orientation of external objects in relation to the body, referred to as egocentric (body-centered) spatial orientation, is fundamental to goal-directed actions. The internal estimates of egocentric spatial orientation can be quantified using the subjective visual body axis (SVBA) task, in which participants align a visual line parallel to the perceived body (longitudinal) axis, and estimation errors are evaluated. It is known that when the whole body is tilted laterally, the SVBA is typically biased towards the body tilt. Previous research (Tani and Tanaka, 2021) showed that gray matter volume in the right middle occipital gyrus (rMOG) correlated with individual SVBA bias induced by whole-body tilt (tilt-dependent error: TE); however, the causal relationship between them remains unclear. To validate this, we employed low-frequency repetitive transcranial magnetic stimulation (rTMS) to the rMOG or right temporoparietal junction (TPJ; as a control site), which can induce a transient suppression of brain activity. Twenty right-handed healthy volunteers [5 women, Mean±standard deviation (SD): 20.3±0.28 years] underwent three TMS conditions (rMOG, rTPJ, or Sham). For each

condition, they performed the SVBA task in both an upright and a laterally tilted position with 10 degrees before and after stimulation. We calculated the rTMS-induced changes in the TE (ΔTE) for each condition by subtracting the TE before stimulation from that after stimulation. The number of participants, protocol, and statistical analysis were pre-registered in the Open Scientific Framework (OSF; https://doi.org/10.17605/OSF.IO/FEU8T). Statistical analysis (repeated-measures ANOVA and pairwise Dunnett test) showed that theΔTEs were significantly smaller in the rMOG condition (-2.65 ± 0.98°; $p = 0.04$) but not in the rTPJ condition (−1.99 ± 1.03° ; $p = 0.15$) than the sham condition (0.20 ± 0.84°), indicating the specific reduction of the tilt-dependent SVBA bias by the rTMS to the rMOG. Our results support the causality of the rMOG in egocentric spatial orientation during whole-body tilt.

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Poster

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Topic: D.05. Auditory & Vestibular Systems

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JST CREST/JPMJCR22P5
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Title: The vestibular stimulus calls back the periodic rhythm of the eye movement acquired by the visual stimulus

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Abstract: The optokinetic response (OKR) is a reflexive eye movement that follows large visual field motion to stabilize the retinal image. Previous research demonstrated the acquisition of a predictive (p)OKR in goldfish following prolonged exposure to temporally periodic visual stimulation (Marsh and Baker, 1997). A recent study further elucidated the crucial role of the cerebellum in the pOKR acquisition and maintenance (Miki et al., 2018). Interestingly, despite possessing similar basic vestibular and cerebellar neural circuitry to goldfish, other animal species such as zebrafish, medaka, and mice exhibited minimal or no pOKR (Miki et al., 2020; Yamanaka et al., 2022). Additionally, animals presenting the pOKR were found to exhibit long lasting optokinetic after nystagmus (OKAN), which is generated in the dark after prolonged constant velocity visual stimulation, while those that did not acquire pOKR showed little OKAN. OKAN is considered a manifestation of the velocity storage mechanism (VSM) which stores eye

velocity signal during visual and vestibular stimulations, and discharges it when the sensory signals are attenuated. These observations led to the conclusion that the VSM is a fundamental determinant in the pOKR acquisition (Miki et al., 2020). Notably, the VSM is shared between the OKR and the vestibulo-ocular reflex (VOR), which is another reflexive eye movement to stabilize visual images during head motion. Consequently, we hypothesized that the predictive ability acquired through visual training in the OKR may transfer to the VOR. In this study, we aimed to test this hypothesis using goldfish. Initially, we provided temporally periodic visual stimulation to the animals, rotating at a velocity of 20 deg/s for 8 s followed by an 8 s pause, continuously for a duration of over 3 hours. The goldfish subjected to this visual stimulation exhibited the acquisition of the pOKR and presented rhythmic eye velocity oscillation at the trained period in the dark. This oscillation decayed away after a certain number of cycles, as demonstrated previously. Subsequently, we provided a vestibular stimulus by rotating the animals at 20deg/s for 1min in the dark. As a result, the decayed rhythmic eye velocity oscillation, acquired through visual training, was reinstated during the vestibular stimulation. This finding suggests that the eye velocity oscillatory rhythm, obtained as the pOKR through visual training, is maintained within the shared neural substrate of the vestibular system, even after the decay of the predictive behavior. Furthermore, this memory can be recalled by vestibular stimulation, exhibiting as the predictive VOR.

Disclosures: **Y. Toshimi:** None. **Y. Hirata:** None.

Poster

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Topic: D.05. Auditory & Vestibular Systems

Support: NIH Grant 1 R21 DC018083-01
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Title: Exploring the benefits and limitations of a bilateral vestibular implant.

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Abstract: Introduction: Vestibular neuroprostheses have limitations when implanted unilaterally. Stimulation current without spread to adjacent end organs is limited. Activation of afferents and secondary vestibular neurons is incomplete. Interleaved stimulation of multiple canal nerves produces nonlinear combinations of resulting eye movements. Amplitude or frequency modulated stimulation produces directionally polarized responses with distorted velocity profiles. It is unclear if this is due to the intrinsic nature of electrical stimulation, or to the limitations of unilateral stimulation per se. To explore this question, we compared unilateral

and bilateral prosthetic stimulation in monkeys implanted with a bilateral vestibular implant.
Methods: We implanted a bilateral vestibular neuroprosthesis in rhesus monkeys. The device consisted of 2 independent UW Cochlear 2x2x2x16 vestibular implants connected to a common controller via two external RF links. In these experiments, the device was computer controlled, providing different combinations of current or frequency modulated input to each ear. Behavior was recorded with the use of 3D scleral coil. Electrical stimulation could be provided in any combination to the 6 canals in both ears, and could occur in association with rotation using a computer controlled multi-axis rotator.
Results: Combined modulated vestibular stimulation of canal pairs produced summation of the vestibular responses elicited by individual semicircular canals or combinations of canals. This was seen with both stepped constant rate/constant current stimuli and with sinusoidal amplitude or frequency modulated stimulation. In addition, the elicited eye movements had dramatically improved symmetry and spectral purity. Although this was most pronounced during out of phase sinusoidal stimulation, the improvement was not contingent on modulation of inputs to both ears, suggesting that combinations of modulated and non-modulated prosthetic vestibular stimulation might prove beneficial in some patients. Furthermore, combination of natural and bilateral prosthetic stimulation in a lesioned monkey produced eye movements which resembled those of fully intact rhesus monkeys.
Conclusions: Bilateral vestibular prosthetic stimulation overcomes many of the limitations imposed by unilateral prosthetic stimulation. The increased risk to hearing of such implants would limit their initial application to patients with vestibular loss but requiring bilateral cochlear implantation, however these patients may significantly benefit from the increased performance of such a device.

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Poster

PSTR276. Vestibular Processing and Perception

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Topic: D.05. Auditory & Vestibular Systems

Support: NIH NIDCD R01-DC018061
NIH T32-5T32DC000023-37

Title: Effects of visual tilt illusion on vestibular sensitivity in the posterior cerebellum

Authors: *L. J. GÓMEZ[1], R. MILDREN[1], F. KARMALI[2], K. CULLEN, 21205[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Otolaryngology, Harvard Med. Sch., Boston, MA

Abstract: The ability to keep our head stable in space requires an understanding of our head's orientation relative to gravity. No sensory system directly encodes gravity; rather, the perception of gravity is an emergent property of the vestibular system, arising from the integration of linear acceleration signals (encoded by the otolith organs) and angular acceleration signals (encoded by the semicircular canals). In the cerebellum, the nodulus and ventral uvula (NU) of the posterior vermis are uniquely situated to perform this integration. Unlike other areas of cerebellar cortex that receive their vestibular input indirectly via the vestibular nuclei, NU also receives robust input directly from primary vestibular afferents. This direct input ensures that vestibular signals are conveyed faithfully to NU so that an internal model of the head relative to gravity can be continuously updated across behavioral contexts. In addition to vestibular inputs, NU also receives neck proprioceptive input (via mossy fibers) and visual motion information (via climbing fibers), both of which are thought to modulate the internal model computed by NU. The response profiles of many NU Purkinje cells clearly encode vestibular and proprioceptive input, which NU likely integrates to update postural reflexes. However, the mechanism by which visual motion information influences activity in NU—and, thus, how visual motion contributes to NU's internal model of gravity—is unknown. To investigate the effect of visual motion information on NU neural dynamics, we performed high-density (128-channel) recordings from NU Purkinje cells in behaving rhesus macaques during a visual tilt illusion paradigm. After priming the macaques with the visual tilt illusion, we examined whether baseline firing rates and responses to vestibular stimulation were altered in the simple spiking activity of NU Purkinje cells. We found that NU neurons did not consistently or appreciably alter their baseline firing rates in response to visual priming, but that visual motion did consistently alter sensitivity to vestibular stimulation. These results indicate that visual motion information does not have an overall modulatory effect on NU Purkinje cell activity; rather, it directly modulates Purkinje cell responses to vestibular input. Together, these results improve our understanding of how the posterior cerebellum uses multiple streams of information to generate an internal model of self-motion relative to gravity.

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Poster

PSTR276. Vestibular Processing and Perception

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Topic: D.05. Auditory & Vestibular Systems

Support: OOAQ-REPAR grant
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Title: Vestibular Rehabilitation in managing the Mal de Debarquement Syndrome: a comprehensive postural control analysis

Authors: *A. PIERRE[1,2], A. CÉDRAS[1,2], K. MOÏN-DARBARI[1,2], K. FOISY[3], S. AUGER[3], D. NGUYEN[4,5], F. CHAMPOUX[1,2,6], M. MAHEU[1,2];

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Abstract: INTRODUCTION. Mal de debarquement syndrome (MdDS) is a rare and poorly understood vestibular disorder that is recognized to significantly impact the quality of life. However, to date, the treatment options remain very limited. Vestibular rehabilitation (VR) is a well-documented, efficient, and widely available treatment option for peripheral vestibular impairment, but its efficacy is poorly known in MdDS. The objective of the study was to explore the influence of traditional vestibular rehabilitation on postural control in a patient diagnosed with MdDS. **METHOD.** Three different participants were assessed: 1- healthy control; 2- participant with identified peripheral vestibular impairment (VI); 3- participant diagnosed with MdDS. Postural control was assessed using a force plate (AMTI-AccuSway) under four conditions: A-Eyes open on firm surface/ B-Eyes closed on firm surface / C-Eyes open on foam/ D-Eyes closed on foam. The center of pressure was recorded and analyzed both in the temporal domain (sway velocity) and the frequency domain (wavelets). Additionally, the perceived handicap using the Dizziness Handicap Inventory (DHI) was assessed. Postural control and Dizziness Handicap Inventory (DHI) were assessed in each participant before (T0) and after (T1) the VR program. The VI participant and the MdDS patient performed a 4-week VR program when the healthy control was assessed twice separated by 1 week without any specific intervention. **RESULTS.** The VI participant showed clear improvement on DHI and sway velocity on condition eyes closed with foam (condition D). Accordingly, a reduction of energy content within frequency bands (0.39Hz-0.78Hz and 0.78Hz-1.56Hz) was observed post-rehabilitation for this participant in both conditions with foam (conditions C and D). Interestingly, the MdDS participant demonstrated a reduction in sway velocity in most of the conditions, but the frequency content was not modified by VR and was comparable to healthy control. Accordingly, the DHI of the MdDS participant failed to demonstrate any difference following VR. **Conclusion.** The results of the present study question the use of vestibular rehabilitation as an efficient treatment option for MdDS. Future studies will have to recruit a larger sample size and focus on the relation between the illusion of movement and postural characteristics such as sway velocity.

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Poster

PSTR276. Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.16/DD10

Topic: D.05. Auditory & Vestibular Systems

Support: Région Normandie grant # 00115524-210E06581
CNES grant # 2023/480001180

Title: Effects of gravity on the perception of rotation and time

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Abstract: While many results highlight the pivotal role of the vestibular system in space cognition only a few studies have shown that the vestibular system plays also a role in the perception of time. During vestibular stimulations, perceived time appears to contract (Utegaliyev et al., 2022) and the perceived timing of sensory input if affected (Binetti et al., 2013).
Weightlessness has also been shown to alter both spatial cognition and time perception. Distances are underestimated when subjects are in weightlessness during parabolic flight (Clément et al., 2008, 2016, 2020) and orbital flight (Clément et al., 2013). We also recently showed that spatial updating, i.e. the ability to estimate new spatial relationships with our surroundings as we move, is impaired during parabolic flights (Stahn et al., 2020).
While in space, astronauts under-produce duration (Navarro Morales et al., 2023; Kuldavletova et al., 2023). We have also found that, during parabolic flights, hypergravity and microgravity affect the reproduction of time intervals (Clément, 2018).
Recent studies have identified common neuronal circuits for judging time and space, suggesting that there may be a single and universal mechanisms in the central nervous system for analysing multiple dimensions, including time, space, numerals, volume, and frequencies (Chen et al., 2021; Cona, 2021; Walsh, 2003).
In weightlessness, as the vestibular system is less stimulated than in normal gravity (due to the absence of tonic otolith inputs) and due to the absence of the gravitational reference, we hypothesize that the cortical network representing spatial and temporal events is disrupted leading to i) alterations in spatial orientation and time perception and ii) that those alterations are correlated with each other.
To test this hypothesis, 18 subjects will be studied in 3 tasks at 1g, 0g and 1.8g during parabolic flights.
During the first task, the participant will be seated on a rotatory chair, and will have to evaluate the amplitude of rotation. During the second task, the participant, while free-floating during weightlessness, will be rotated around the yaw, roll or pitch axis and will have to evaluate the amplitude of rotation.
During the third task, a square will be displayed for 2 to 10 seconds (encoding) and after a few seconds, the square will reappear and subjects will have to judge when the previously displayed duration has been reached (reproduction). As we want to test if different levels of gravity will yield discrepancies between the evaluation and reproduction phases, the encoding will be applied during one gravity level and the reproduction will occur in another gravity level.

Disclosures: O. Kuldavletova: None. **D. Navarro-Morales:** None. **G. Quarck:** None. **P. Denise:** None. **G. Clément:** None.

Poster

PSTR276. Vestibular Processing and Perception

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.17/DD11

Topic: D.05. Auditory & Vestibular Systems

Support: NIH R01DC01379801A1

Title: Transient Changes in Sound-Evoked Vestibular Myogenic Potentials in a Preclinical Model of Noise Overexposure

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Abstract: The vestibular system, located in the inner ear, plays a crucial role in providing critical input for balance and posture by encoding changes in head rotation, translation, and gravity. Similar to the cochlea, the vestibular end organs also respond to loud acoustic stimuli, with the saccule and utricle being particularly susceptible to damage caused by hazardous noise or blast exposures. Over the years, extensive pre-clinical work has characterized the noise-induced changes in the morphological and functional features of the otolith organs using a combination of imaging techniques and the study of vestibular short-latency evoked potentials (VsEPs). However, due to challenges in recording VsEPs in humans, the clinical assessment of vestibular function in noise-exposed subjects rather relies on the analysis of vestibular evoked myogenic potentials (VEMPs). Although prior work has elucidated the neural basis of VEMPs, their use in preclinical studies to characterize the pathophysiology of vestibular dysfunctions has been limited, primarily due to the low level of reproducibility and high variability of the responses elicited in animal models so far. In this study, we employed a standardized preclinical cVEMP setup and test protocol developed by our group that closely mimics clinical methodologies. We provide a detailed characterization of cVEMPs evoked in noise-exposed rodents. Male Brown Norway rats (14-18 weeks) with normal hearing and vestibular function were screened using a Smart EP evoked potentials system (Intelligent Hearing Systems, USA). The animals were then exposed to broadband noise (4-16 kHz) at 110 dB SPL for 1 hour. Changes in thresholds, amplitude, and latency of auditory brainstem responses (ABRs) and cervical vestibular myogenic potentials (cVEMPs) evoked by pure tone bursts at 1 and 8 kHz were compared to baseline (pre-trauma) at multiple time-points up to 84 days post-noise. Within the cohort studied, measurements of auditory function showed a permanent threshold shift (PTS) following noise trauma. In contrast, cVEMP assessments at both frequencies tested revealed noise-induced temporary threshold shifts that recovered by Day 7. We also observed transient reductions in amplitude and increases in latency of vestibular responses to 90 dB SPL stimuli at 1 and 8 kHz, with full recovery by Day 28 and Day 14 respectively. The results of this study suggest that cVEMPs represent a reliable non-invasive diagnostic test in a preclinical setting, with significant implications for understanding early and long-term changes and potentially identifying the neural basis of vestibular disorders, including noise-induced vestibular deficits.

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Poster

PSTR276. Vestibular Processing and Perception

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Program #/Poster #: PSTR276.18/DD12

Topic: D.05. Auditory & Vestibular Systems

Support: NIH R01 DC2390

Title: Rapid gaze-shift adaptation during self-generated vestibular prosthetic stimulation

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Abstract: The brain must differentiate between externally-generated and self-generated sensory inputs to build stable perception and generate appropriate behavior. Specifically for vestibular prosthesis users, the brain must learn to utilize prosthetic vestibular input to maintain visual and postural stability while also suppress/cancel these reflexes when they are counterproductive to behavioral goals. Here, we leveraged a gaze-shift task—a naturalistic behavior that requires the gating/canceling of vestibular input—to directly investigate how self-generated prosthetic stimulation affects reorientation behaviors. In a monkey with bilateral vestibular deficits, we implanted a vestibular prosthesis that senses head rotation and transforms this movement into vestibular nerve stimulation, substituting for the damaged periphery. The monkey was trained to make eye-head coordinated gaze shifts between horizontal targets while the head, eye, and gaze positions were recorded. Each session comprised a three-block learning paradigm: baseline gaze-shifts, gaze-shifts with prosthetic stimulation, and washout without stimulation. We hypothesized that 1) prosthetic stimulation would first engage vestibular reflex pathways, resulting in impeded head movements and truncated gaze-shifts but also that 2) the brain would then adapt to this new sensory input and no longer engage the reflex when it is counterproductive. Consistent with our predictions, gaze position error initially increased after stimulation onset and then exponentially decayed within ~90 trials. Prosthesis-evoked vestibulo-ocular reflex (VOR) gain and change in head position impeded by the prosthesis-evoked vestibulo-collic reflex (VCR) showed a similar decay though both at a slower rate (~200 trials), suggesting that the suppression/canceling of VOR and VCR both contributed to the observed improvement in gaze accuracy. In addition, early washout trials and catch trials during learning showed oppositely-directed gaze position error, indicating a central adaptation in addition to the observed reflex suppression/cancellation. This central adaptation could be due to the updating of the gaze controller or the updating of a forward internal model to predict and cancel self-generated prosthetic sensory input. Together, these results show that the brain can quickly adapt to self-generated prosthetic stimulation to improve behavioral performance. Importantly, these findings provide new insights on how prosthetic inputs interact with different vestibular pathways in a context-specific way.

Disclosures: **K. Wiboonsaksakul:** None. **C.C. Della Santina:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Labyrinth Devices, LLC. **K.E. Cullen:** None.

Poster

PSTR276. Vestibular Processing and Perception

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Program #/Poster #: PSTR276.19/DD13

Topic: D.05. Auditory & Vestibular Systems

Support: NIH 1F31DC020910-01A1

Title: Early developmental contributions to directional tuning of the gaze stabilization circuit in the larval zebrafish

Authors: ***P. LEARY**[1], D. GOLDBLATT[2], K. HAMLING[1], D. SCHOPPIK[1];
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Abstract: All vertebrates stabilize gaze with a simple circuit that transforms sensed head/body tilts into corrective counter-rotations of the eye. While it is known that the central vestibular nucleus of this circuit is indispensable for encoding directionally-specific stimuli, the factors influencing development of directional tuning are unknown. To investigate the maturation of directional sensitivity in the gaze stabilization circuit, we first measured longitudinal responses of birthdated central vestibular neurons to body tilts. We found that at 3 dpf, directional tuning is present in the earliest-born neurons but not the latest-born neurons. Following 3 dpf, the directional sensitivity of earliest-born neurons strengthens up to 5 dpf, while the directional sensitivity of the latest-born neurons strengthens up to 7 dpf. These results indicate that directional tuning is acquired and matures in a time-dependent manner. To investigate whether this tuning is present immediately upon neuronal birth or if it is acquired over time, we measured birthdated neural activity in response to body tilts directly after the entire vestibular nucleus became post-mitotic (53 hpf). At this time point, we found that all vestibular neurons are responsive to body tilt stimuli, but in an untuned fashion. By 72 hpf, the earliest-born cells show evidence of directional tuning. These findings demonstrate that a period of time exists in which responsive, untuned vestibular neurons acquire directional tuning. Over time, vestibular neurons strengthen their directional tuning as a function of birthdate. Ongoing sensory perturbation experiments during this window of tuning acquisition will reveal whether tuning properties are predetermined or dependent on proper sensory input during early development. Together, these findings will reveal how early development shapes the capacity of a sensorimotor circuit to stabilize gaze.

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Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

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Topic: D.06. Vision

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American Diabetes Association Pathway to Stop Diabetes Initiator Award 1-18-INI-14 to J.N.C

Title: A comparative molecular atlas of tree shrew and mouse superior colliculus neurons

Authors: *Y. LIU[1], J. A. MCDANIEL[1], E. L. SAVIER[2], J. CANG[1], J. N. CAMPBELL[1];
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Abstract: The superior colliculus (SC) is a conserved midbrain structure, with its superficial layers (sSC) manifesting diverse visual responses and playing important roles in visual coding. Although the anatomy, connectivity, and function of the SC have been studied in many species, the degree to which molecular cell types and neural circuits are conserved remains unclear. To address this question, we performed single-nucleus RNA-sequencing (snRNA-seq) of both tree shrew and mouse sSC. While the mouse is more genetically tractable, the tree shrew is a better model for vision research given its advanced visual capacity and closer phylogenetic affinity to primate. We compared gene expression across tens of thousands of sSC neurons from the two species and unbiasedly classified 31 neuronal populations. Inhibitory neurons were enriched in the sSC of both species in terms of molecular subtypes and cell numbers, and they shared similar spatial distribution across depth. Furthermore, the majority of neuron subtypes were conserved between the two species, with some differing in abundance. Next, we compared gene expression between neuronal populations and anatomically mapped differentially expressed genes by fluorescence in situ hybridization (FISH). We found that some conserved cell types differed in expression of certain genes between the two species. Finally, we detected a distinct neuron subtype found in the tree shrew sSC but not in mouse, an inhibitory subtype restricted to the surface of the sSC. Together, our comparative molecular taxonomy of sSC neuron subtypes reveals molecular and cellular differences between tree shrews and mice which could underlie functional differences in visual processing. This information may provide insights into the evolution of SC function, connection, and development across species.

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Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

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Topic: D.06. Vision

Support: NIH Grant R01EY026286
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Title: Spatiotemporal Receptive Fields of Superior Colliculus Neurons in Tree Shrew and Mouse

Authors: *C. LI[1], S. TANABE[1], E. L. SAVIER[2], H. CHEN[1], P. B. SEDERBERG[1], J. CANG[1]; [1]Univ. of Virginia, Charlottesville, VA; [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Tree shrews (Tupaia belangeri) have shown great potential as an animal model for visual studies. They are diurnal animals with well-developed visual systems that are closer to primates than mice, and also offer more practicality than primates for laboratory-based studies. The success in applications of modern genetic, viral, and pharmacological techniques further opens up possibilities to study neural mechanisms of vision using tree shrews. However, our understanding of how the superior colliculus (SC) of tree shrews, a key visual processing center that receives direct retinal ganglion cell projections, responds to stimulus still largely rests upon studies from decades ago where traditional stimuli such as gratings and spots were used. These stimuli rely heavily on the prior knowledge we learned from other structures, and limit the investigation of broader feature space and spatiotemporal integration. Here we designed a more comprehensive set of visual stimuli including spatiotemporal white noise variants to compare the visual response properties of the SC in both awake tree shrews and mice. We recorded single-unit spikes using a 64-channel silicon microprobe. Measuring the spatiotemporal receptive fields with a sparse noise stimulus, our results show that the visual layers of the tree shrew SC have smaller receptive fields compared to mice on average, with a greater prevalence of center-surround substructures. In addition, the response latency of the tree shrew SC is very short (25-50 ms) compared to that of mice (60-80 ms). Furthermore, a noise stimulus that is denser than sparse noise resulted in smaller receptive fields in tree shrews, but not in mice, thus suggesting a higher level of nonlinear spatial interaction in tree shrews. To summarize, our study revealed differences in the SC visual response properties of tree shrews and mice, providing an evolutionary perspective on SC functionality for encoding visual information of their respective environment.

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Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

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Title: Asymmetrical retinotopic and category non-selective fMRI maps in macaque superior colliculus

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Abstract: The superior colliculus (SC) of both humans and monkeys contains topographic maps of different sensory and motor modalities which are used to guide (c)overt orienting behavior. Whereas an orderly representation of polar angle is well-documented, some controversies exist concerning (para-)foveal and far-peripheral eccentricity representations in primate SC. Previous monkey electrophysiology studies also reported distinct patterns of activity for behaviorally relevant stimulus categories. Here, we used sub-mm and conventional resolution fMRI to test for category-selectivity and to perform small- and wide-field retinotopic mapping of the SC in macaques. In seven monkeys we performed phase-encoded retinotopic mapping fMRI experiments at 3T, with 0.6mm (n = 3) and 1.25mm (n = 4) isotropic voxels. The stimuli consisted of slowly moving apertures (rotating wedges and expanding/contracting rings) superimposed on high-contrast, dynamic, colorful, and multi-object textures - covering either 80° (n = 2), or 25° (n = 5) of the visual field. In a separate passive-viewing fMRI experiment (n = 2), we presented spatially restricted stimuli (15° diameter on average) at different locations (center, and at 17° eccentricity in the lower left/right quadrants), consisting of luminance-matched monkey faces, bodies, objects, and their phase-scrambled versions. We obtained clear retinotopic maps of the SC in five animals. The polar angle and eccentricity maps revealed features consistent with previously reported fMRI maps in humans and electrophysiological findings in monkeys. Contralateral upper and lower quadrants are represented in medial and lateral parts of the SC, respectively. Moreover, the central and peripheral parts of the visual field are represented rostrally and caudally, respectively. Surprisingly, the representation of para-foveal fields differed between left and right SC in all five monkeys, being largely confined to the left colliculus. This

effect cannot be explained by interhemispheric differences in SNR of the fMRI signal. Furthermore, the responses to spatially-restricted stimuli confirmed this asymmetrical topographical representation but did not reveal category selective responses in the SC. In conclusion, our fMRI study demonstrates that the macaque superior colliculus harbors wide-field retinotopic maps, with no evidence for fMRI category specialization, but showing a surprising interhemispheric asymmetry in its retinotopic organization.

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Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR277.04/DD17

Topic: D.06. Vision

Title: Direction selectivity during self-generated visual motion in the mouse superior colliculus

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Abstract: Direction selective (DS) neurons play a crucial role in motion processing within the early visual system. However, their response to visual motion generated by the animal's own movement, known as optic flow, remains poorly understood. Similarly, how early DS neurons encode foreground object motion on a background of self-generated global motion is largely unknown. To address these fundamental questions, we investigated the responses of neurons in the mouse superior colliculus (SC) to visual stimuli in a virtual reality (VR) environment. Using *in vivo* two-photon Ca^{2+} imaging, we studied DS neurons in the superficial lamina of the mouse SC. We simulated a virtual corridor by projecting computer-generated images onto a dome surface. The walls and ceiling of the corridor were textured with random dots. We conducted both "closed-loop" and "open-loop" sessions to examine the neural response. In the closed-loop sessions, the rotation of a treadmill was coupled to the movement in the virtual corridor, allowing mice to self-generate visual flow feedback during locomotion. In the open-loop sessions the virtual corridor moved independently of the animal's locomotion. Additionally, moving dots (eight directions) were presented in a circular patch (30° or 40° diameter) either on a gray background or within the virtual corridor during both closed-loop and open-loop conditions. First, we compared the responses of neurons between presenting a patch on a gray background and a patch during a closed-loop session. Our results revealed that the preferred direction of DS neurons remained unchanged regardless of the background type. However, the global direction selectivity index (gDSI) of these neurons increased during closed-loop sessions. Subsequently, we compared the response properties of DS neurons between open-loop and closed-loop sessions. No significant differences were observed in terms of preferred direction or

gDSI between these two conditions. These preliminary findings suggest that DS neurons in the superficial SC are modulated by visual background but unaffected by locomotion or optic flow. These neurons appear responsive to local but not global motion cues, including those generated by self-movement. By harnessing a VR environment, we gained novel insights into how DS neurons in the mouse SC respond to visual stimuli during naturalistic behaviors.

Disclosures: H. Chen: None. **V. DePiero:** None. **E.L. Savier:** None. **J. Cang:** None.

Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

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Topic: D.06. Vision

Support: NIH Grant K99/R00 EY031783 (to E.S.)
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Title: Characterization of visual response properties and connectivity of Wide-Field Vertical neurons in the mouse superior colliculus

Authors: *E. L. SAVIER[1,2], H. CHEN[2], J. CANG[3];
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Abstract: Vision is a sense that serves many different ethological functions across species. Visual information can be used to either detect preys or predators, and therefore generate orienting or escaping responses. The superior colliculus has been implicated in the orchestration of these behaviors. Within this structure, at the interface between the primary and the secondary visual pathway, lay the wide-field vertical neurons (WFV). WFV are a conserved morphologically defined cell-type found across many taxa from reptiles to highly visual mammals, independently of their visual ecology. These neurons display wide arborization and typical bottlebrush distal tips which form connections with retinal ganglion cells axonal terminals. In mammals, these neurons receive direct inputs from the retina and the primary visual cortex, and have the pulvinar as a known target, however, their brain-wide connectivity remains to be identified. These cells display peculiar response properties, but despite their ubiquity and unique morphology, their contribution to vision remains elusive.In this study, we have characterized WFV morphology, connection, and visual response properties in vivo in the laboratory mouse. Two-photon calcium imaging in awake mice using a transgenic Cre-line targeting specifically WFV (NTSR1-Cre) confirmed their unique response properties. WFV showed a strong preference for small moving stimuli and a slight bias for certain directions. Interestingly, visual responses showed strong modulation by locomotion, which is in contrast with what has been observed for superficial direction selective neurons in the SC. In addition, Cre-dependent rabies tracing unraveled a variety of sources of input which had not been

described previously.These results place WFV as a major integrator of visual information in the superior colliculus. Their modulation by locomotion and direction selectivity suggests a role in the integration of non-visual signals which might be linked to the processing of optic flow. Taken together, this initial characterization paves the way to elucidate the role of these neurons in guiding visual behavior.

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Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR277.06/DD19

Topic: D.06. Vision

Support: 1ZIAEY000570-01

Title: Neurons in the primate superior colliculus are selective for binocular disparity

Authors: I. KANG[1], G. YU[1], L. N. KATZ[1], R. J. KRAUZLIS[1], *H. NIENBORG[2];
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Abstract: The superficial layers of the superior colliculus (SC) get prominent inputs from the visual cortex, where many neurons are selective for horizontal binocular disparity, a powerful cue for depth perception. Despite this strong binocular input to the SC, selectivity for binocular disparity has never been studied in the primate SC.
Here, we used multichannel linear arrays to record neurons in the superficial and intermediate layers of the SC of one rhesus macaque who had no prior training on disparity-based tasks. The monkey passively viewed random dot stereograms (RDSs) presented in the neurons' receptive fields (RF). The circular RDSs consisted of a disparity-varying central disc and a surrounding annulus at zero disparity. The eccentricity of the visual RFs ranged from foveal to peripheral (0.7 to 40.3°, mean±sd = 13.7±9.5°). Of the 193 isolated neurons, 121 units (63%) were significantly selective for binocular disparity (Disparity Discrimination Index, Prince et al., 2000, permutation test, mean±sd = 0.66±0.13). For most of these (93%) disparity tuning was well described by a Gabor function (explaining at least 60% of the variance, mean±sd = 82±60%). The tuning was typically even-symmetric: 88% were classified as tuned-excitatory (n=71) or tuned-inhibitory (TI, n=28), and the rest classified as Far (n=8) or Near (n=6) cells (Read and Cumming, 2003). The preferred disparity was broadly distributed around zero. Units recorded in the same session tended to prefer the same disparity sign suggesting clustering for disparity selectivity across SC layers. There was a positive correlation between the absolute preferred disparity and the RF eccentricity ($r = 0.38$, $p < 10^{-3}$, n=85, TI cells were excluded), and the tuning width ($r=0.44$, $p < 10^{-5}$, n =80), but no bias depending on whether the RF was in the lower or upper visual field ($p=0.98$, t-test). For all units, we also measured the response to anti-correlated RDSs (i.e., black

dots in the image of one eye were white in the image of the other eye, vice versa) and found the tuning tended to be inverse of that for the correlated RDSs albeit with a weaker amplitude and larger response variability. Lastly, SC neurons were functionally classified based on their responses during memory-guided saccades, but we found no difference in tuning strength across SC cell classes ($p = 0.37$ across 6 classes, ANOVA).
Overall, SC neurons possess selectivity for binocular disparity which shares many similarities with that of cortical neurons, especially of V1. This provides a plausible neural substrate for how the SC supports visual orienting in 3D natural environments.

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Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

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Topic: D.06. Vision

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Title: Reward modulates visual responses in mouse superior colliculus independently of arousal

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Abstract: The processing of sensory input is constantly adapted to behavioural demands and internal states. Obtaining reward satisfies such behavioural demands and associating the reward with its source, a certain environment or action, is paramount for survival. Here, we show that water reward increases subsequent visual activity in the superficial layers of the superior colliculus (SC), which receive direct input from the retina and belong to the earliest stages of visual processing.
We trained mice in a visual detection task that required them to detect a stimulus of varying contrast in the left or right visual field. The mice had to interactively move the stimulus towards the centre of the visual field or refrain from movement in case of no stimulus. Correct choices were rewarded with water, incorrect choices were followed by auditory noise. We then used two-photon calcium imaging to record activity of neurons in the superficial SC (sSC) of 6 well-trained mice in a total of 22 sessions.
We quantified the effect of various task behaviours and pupil-linked arousal on the gain of the contrast tuning curve. Similar to previous studies, we found that arousal modulated the visual responses of sSC neurons, leading to increased and decreased activity in different neurons.

Additionally, we discovered that visual responses of about 20% of sSC neurons increased after reward delivery in the previous trial. Modulation by reward, but not arousal, significantly improved the performance of a population decoder to detect visual stimuli. The effect of previous reward on visual responses was independent from modulations by pupil-linked arousal and could not be explained by eye movements/position, licking, whisking, wheel turns, slow fluctuations in neural responses across trials, or reward history.
Lastly, we validated our results using electrophysiology with Neuropixels probes in 6 separate well-trained mice. By recording from the entire depth of the SC, we discovered that 26% of visually responsive sSC neurons were reward-modulated compared to 18% in the dSC. In contrast, 10% of visually responsive sSC neurons were modulated by arousal compared to 13% in dSC.
Our findings show that visual responses of sSC neurons are strongly influenced by two independent state variables: pupil-linked arousal and previous reward. Future studies may reveal how these non-visual modulations help downstream processes in guiding behaviour.

Disclosures: L.J. Baruchin: None. **M. Alleman:** None. **S. Schröder:** None.

Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.08/DD21

Topic: D.06. Vision

Support: 1F32EY032776
NSF CAREER 2047298

Title: Relative salience-dependent stimulus competition in the mouse superior colliculus

Authors: *S. MYSORE[1], N. B. KOTHARI[2], E. SCHURINK[3];
[2]Psychological and Brain Sci., [3]Undergraduate Program in Neurosci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: Selecting the most salient (or more generally, the highest priority) stimulus for subsequent neural processing is a critical component of spatial selective attention and adaptive behavior. For such target selection for spatial attention, it is well-established that competitive interactions among stimulus representations in the intermediate and deep layers of the superior colliculus (SCid), a midbrain sensorimotor hub, are critical. However, little is known about the rules governing the relative-salience dependence of competitive interactions in the mammalian SCid. Here, drawing inspiration from work in owls, we recorded extracellular responses of SCid neurons in passive head-fixed mice viewing single and competing stimuli. Mice were presented with one visual stimulus inside the receptive field (S_{in}) and another competing stimulus far outside (S_{out}). The salience of S_{out} was systematically varied, while that of S_{in} was held constant, and the resulting competitor salience-dependent response profiles of SCid neurons were

analyzed. We found several notable results. First, we found that firing rates of SCid neurons were negatively correlated with increasing salience of the competitor and these profiles were well fit by sigmoidal functions. Second, we found that a sizeable number of neurons encoded relative salience with an abrupt switch-like transition from high to low firing rates, while the remaining had a more gradual transition. Third, and importantly, we found that, on average, the value of competitor salience at which the responses transitioned from high to low values, the transition value, was equal to the salience of S_{in} (i.e., when relative salience was zero). Indeed, when the strength of S_{in} was increased, the transition value also increased by the same amount, revealing that SCid neurons signal accurately whether or not the stimulus inside their receptive is the most salient. Separately, we examined whether these properties of signaling of the most salient stimulus depended on rostro-caudal and medio-lateral location of the neuron's receptive field. Combined, our results demonstrate that the mammalian SCid accurately, precisely and flexibly signals the most salient stimulus across space.

Disclosures: S. Mysore: None. **N.B. Kothari:** None. **E. Schurink:** None.

Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.09/DD22

Topic: D.06. Vision

Support: NIH Grant 2R01EY027718
Provost's Undergraduate Research Award

Title: Population signaling of the most salient stimulus in cluttered scenes by neurons across the optic tectum space map

Authors: *S. MARTIN, G. T. ANANDAN, J. H. HUNTLEY, S. P. MYSORE;
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Abstract: The superior colliculus (SC, called optic tectum, OT, in birds) is a midbrain sensorimotor hub known to play a critical role in selective visuospatial attention. Specifically, competitive interactions among the representations of stimuli in the intermediate and deep layers of the SC (SCid/OTid) are critical for the selection of a target among distracters. Thus far, studies of the neural correlates of selection in the SCid/OTid have focused predominantly on competitive interactions among two competing stimuli, with a few exceptions. In one study, it was shown in monkeys that SCid responses decrease systematically as the number of competing distractors increases. Separately, ongoing work in our lab in the barn owl OTid shows that in addition to the overall reduction in the evoked responses, there is also an impairment in the accuracy with which individual SCid neurons signal the most salient among competing stimuli, as the number of competing stimuli increases. Inspired by work in other brain areas (including the OTid of owls), here, we wondered whether population signaling by the OTid network is also

similarly impaired, or whether it might allow improved signaling accuracy as the number of competitors increases. We tested this hypothesis with electrophysiological experiments in the barn owl OTid in conjunction with multi-stimulus competition protocols. Our results suggest that signaling of the most salient stimulus by the OTid network is more accurate than that by individual OTid neurons, particularly as the number of competing stimuli increases. The measured responses also suggest a potential computational mechanism for this improvement in the network signaling accuracy. Together, our results shed new light on the neural basis of stimulus competition in complex, cluttered scenes with greater than 2 stimuli.

Disclosures: S. Martin: None. **G.T. Anandan:** None. **J.H. Huntley:** None. **S.P. Mysore:** None.

Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.10/DD23

Topic: D.06. Vision

Support: R01EY027718

Title: Cholinergic modulation of Imc neural response properties

Authors: *L. ZHANG[1,2], S. P. MYSORE[3];
[1]Neurosci., [3]Johns Hopkins Univ., [2]Johns Hopkins Univ., Baltimore, MD

Abstract: The Imc, a conserved group of inhibitory neurons in the vertebrate midbrain tegmentum, is interconnected bidirectionally with the midbrain sensorimotor hub, the optic tectum (OT; or superior colliculus, SC, in mammals). It is known to control long-range competitive interactions among the representations of stimuli in the OT/SC, which, in turn are critical for the control of selective spatial attention. Indeed, the Imc exhibits a special pattern of donut-like connectivity with the OT - it receives glutamatergic drive from focal portions of the OT space map but sends broad GABAergic projections back across all locations of the OT space map except the ones from which it receives input. This unique pattern of connectivity is responsible for OT's ability to signal the strongest of competing stimuli categorically and reliably. Despite these detailed insights about Imc from the literature, several aspects of Imc function still remain mysterious. Specifically, on the one hand, it is widely believed that Imc receives excitatory input (as glutamatergic drive) solely from the OT. On the other hand, some histological findings in the literature indicate an intriguing localization of acetylcholinesterase to the Imc, suggesting the presence of cholinergic synapses as well on Imc neurons. Whether this staining indeed represents functional cholinergic input onto Imc neurons, and if so, what the functional role of this cholinergic input may be, are unknown. Here, we measured evoked responses of owl Imc neurons extracellularly without and with selective and reversible iontophoretic inactivation of cholinergic inputs. We found that cholinergic input powerfully and

multiplicatively amplified both evoked and spontaneous Imc responses. Our results are consistent with a presynaptic modulation of excitatory drive onto Imc neurons by acetylcholine. Additionally, we find that perturbation of cholinergic input onto Imc produces a modulation of the strength of response suppression in the OTid. This cholinergic modulation of Imc neurons may represent a novel mechanism for modulating signaling by OTid neurons.

Disclosures: L. Zhang: None. **S.P. Mysore:** None.

Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.11/DD24

Topic: D.06. Vision

Support: NIH grant EY022577

Title: Corticotectal encoding of visual information

Authors: *D. CASSATARO[1], E. M. CALLAWAY[2];
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Abstract: An organism makes decisions based on a combination of cognitive and sensory information. How the brain combines, prioritizes, and uses information for organismal goals are major questions in systems neuroscience. The superior colliculus (SC) receives cortex-wide inputs and encodes features and spatial coordinates of points of interest within the space immediately surrounding the organism, with superficial SC responding to sensory features and deep SC signaling its motor outputs. More mysterious is the influence of the prefrontal cortex (PFC) on SC responses; PFC information tends to be abstract, cognitive, and non-spatially-mapped. We hypothesize that SC neurons play a role in spatially mapping potential cognitive information from PFC alongside sensory and motor information. To investigate this, we record neuronal activity from the SC and PFC using multi-shank silicon microprobes while mice perform a visuo-spatial two-alternative forced choice task. Here, we show visual responses of SC neurons and how they are influenced by behavioral variables, visual features, and spatial location of relevant and irrelevant stimuli. We also show how the encoding of these variables changes across the superficial, intermediate, and deep anatomical regions of the SC.

Disclosures: D. Cassataro: None. **E.M. Callaway:** None.

Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.12/DD25

Topic: D.06. Vision

Support: NIH Grant R01NS121919-01
NIH Grant UF1NS116377

Title: The impact of natural movement on visual processing in the mouse superior colliculus

Authors: *S. L. SHARP, D. M. MARTINS, C. M. NIELL;
Univ. of Oregon, Eugene, OR

Abstract: Vision is a dynamic process that involves sampling of the visual scene and exploring the environment through eye, head, and body movements. Traditionally, vision in animal models has been studied through non-natural laboratory paradigms, such as under anesthesia or during awake head-fixation. These approaches have experimental benefits such as precise control of behavior and of the visual input. However, it cannot be ignored that studying vision while constraining movement, as in head-fixation, severely limits our understanding of neural computations that occur during natural vision. Previous research in head-fixed mice has shown that two major brain regions involved in visual processing, primary visual cortex (V1) and superior colliculus (SC), both show neural modulation in response to locomotion, with greater gain modulation in V1 as compared to SC. Recently we implemented methods to study the impact of natural movement on visual processing in V1 of freely moving animals, using chronically implanted high density electrodes combined with head-mounted cameras to measure eye movements and the visual scene from the animal's perspective. We found modulation by head/eye position and an impact of eye movements on temporal dynamics. Here we extend this to superior colliculus in order to investigate natural movement modulation in both visual and multimodal layers of SC. We have demonstrated the ability to successfully record large populations of SC neurons in freely moving animals, measure visual responses, and assess the impact of head, eye, and body movements. This data will allow us to determine how natural movement modulates activity across the layers of SC, from sensory input to motor output.

Disclosures: S.L. Sharp: None. **D.M. Martins:** None. **C.M. Niell:** None.

Poster

PSTR277. Visual Responses in Superior Colliculus and Associated Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.13/DD26

Topic: D.06. Vision

Support: ISF Grant 1684/20
CIDR
JBL

Title: Choosing their battles: developmental improvement in zebrafish hunting behavior

Authors: *M. MOSHKOVITZ, S. SHAPIRA, S. TISHBY, Y. RUBINSTEIN, I. LIFSHITZ, L. AVITAN;
Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Goal directed behavior consists of a sequence of actions performed by the organism in order to achieve a desired target. These sequences often become more efficient as the organism gains experience interacting with the world. It remains unknown what features of the interaction with the external world change with experience. To address this question, we recorded freely swimming developing larval zebrafish (5-15 dpf) while hunting Paramecia using a high-speed camera (500 fps). By tracking the features of the fish and all paramecia in the dish, we found that placing the target in the strike zone does not guarantee a successful event (hit). The complexity of the visual field plays a role in determining the outcome of the event (hit/miss/abort). Over development fish select sparser scenes to initiate their hunt events, and more efficiently handle complex visual scenes. These results form the basis to uncover the neural mechanism mediating the improvement in hunting behavior.

Disclosures: M. Moshkovitz: None. **S. Shapira:** None. **S. Tishby:** None. **Y. Rubinstein:** None. **I. Lifshitz:** None. **L. Avitan:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.01/DD27

Topic: E.01. Eye Movements

Title: Learning when to look: saccade target selection and timing in dynamic environments

Authors: *S. RENGARAJAN, H. SUNDARAM, L. CHUKOSKIE;
Northeastern Univ., Boston, MA

Abstract: Humans use gaze to actively explore the surrounding environment. Timing gaze behavior to environmental events is essential to respond promptly and accurately to fleeting stimuli. Furthermore, the ability to capture and assimilate temporal information about the environment permits predicted responses to future time-limited events. This type of behavior is especially important in tasks embedded in dynamic environments such as ball sports, video games, and even many types of social interaction. When exposed to visual rhythms, such as oscillating patterns, humans are able to synchronize their saccadic eye movements with the temporal structure of the stimuli. This synchronization allows our gaze to align with moments of peak relevance or saliency in the visual scene. By coordinating with the rhythm, saccades optimize the allocation of attention and facilitate efficient information processing. Although we know quite a bit about the spatial deployment of gaze and how we learn where to look in a novel environment (see for example Chukoskie, et al., PNAS 2014), we know considerably less about

how humans learn when to deploy their gaze in dynamic environments. To fill this gap in our knowledge, we designed a paradigm in which saccade targets are defined on the basis of when they occur, not where they occur. Participants engaged in a gaze timing task that required them to identify target bubbles among distractors by shifting their gaze to bubbles that appear at a particular frequency, ignoring bubbles oscillating at distractor frequencies. We use eye tracking to make the paradigm gaze-contingent, such that a correct target selection will be recognized immediately after fixation. We characterize learning through target accuracy, and latency to acquire targets over time. We will also investigate the extent to which saccades entrain to different types of visual rhythms. By analyzing eye movement data in conjunction with psychophysical measurements, we will quantify the temporal dynamics of saccadic synchronization and examine how it influences perception and attentional processes. Future work will relate the behavior of neurotypical participants to participants on the autism spectrum who have in other work exhibited differences in generating well-timed responses to dynamic stimuli and accurately generating predictive behaviors for upcoming events.

Disclosures: S. Rengarajan: None. **H. Sundaram:** None. **L. Chukoskie:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

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Program #/Poster #: PSTR278.02/DD28

Topic: E.01. Eye Movements

Support: NIH grant R01EY022854
CORE Grant P30EY08098

Title: Temporal sources of endpoint error in interceptive saccade to moving target

Authors: *Z. XIAO[1], F. YANG[2], C. BOURRELLY[3], S. WILLETT[3], J. MAYO[4], N. GANDHI[2]; [1]Ctr. of Neurosci., Univ. of Pittsburgh, PITTSBURGH, PA; [2]Bioengineering, [4]Dept of Ophthalmology, [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: To achieve spatiotemporal accuracy in generating saccades towards moving targets, the brain needs to compensate for sensorimotor delays and accurately predict the target's location at the movement end. Previous studies have demonstrated that interceptive saccades account for target velocity and displacement. Notably, the movements exhibit reduced peak velocity and increased ending error compared to matched saccades toward stationary targets. The underlying factors contributing to this degradation need further investigation, as it will facilitate our understanding of how eye movement system responds differently between dynamic and stationary environments. In the current study, we are interested in how delays in sensory-motor integration affect the endpoints of interceptive saccades. A preliminary analysis was conducted on two macaque monkeys during horizontal, leftward saccades. We found that while saccadic latencies towards inward-moving, outward-moving, and stationary targets were in a similar

range, the magnitude of saccadic ending error increased as a function of reaction time in most moving target conditions. This relationship between reaction time and endpoint error was not observed when the target was stationary. The relation between ending error and reaction time was also a function of target velocity. These results suggest that sensorimotor processing time may contribute to the accuracy of interceptive saccades. We hypothesize that longer processing time is associated with degraded target motion processing, thereby increasing movement output error. To more rigorously examine the initial findings and test this hypothesis, we have designed an experimental paradigm that minimizes the influence of target displacement and saccadic amplitude on the ending error and instead isolates the temporal factor. In the second experiment, human participants will be required to make interceptive saccades toward a target moving along a circular path. Since the target eccentricity remains constant during motion, participants' ideal saccadic amplitudes will remain unchanged and independent of the targets' displacement. We expect that as processing time increases, the initial saccade direction will exhibit a larger deviation (until the neural processing resets). Saccade ending error will also be positively related to processing time.

Disclosures: Z. Xiao: None. **F. Yang:** None. **C. Bourrelly:** None. **S. Willett:** None. **J. Mayo:** None. **N. Gandhi:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.03/EE1

Topic: E.01. Eye Movements

Support: JSPS KAKENHI Grant-in-aid for Young Scientists (Grant Number JP20K19549)

Title: Moving target prediction: deciphering gaze and low beta EEG patterns in pursuit and saccade visual strategies

Authors: *R. KOSHIZAWA[1], K. OKI[2], M. TAKAYOSE[3];
[1]Nihon Univ. Col. of Econ., Tokyo, Japan; [2]Nihon Univ. Col. of Sci. and Technol., Chiba, Japan; [3]Nihon Univ. Col. of Industrial Technol., Chiba, Japan

Abstract: Accurate prediction of the trajectory, position, and time of arrival of a ball is of importance in ball sports, such as bat or racket sports. Although some studies have attempted to predict the trajectory, position, and time of arrival of a parabolic moving target, there is a lack of research regarding the brain processing involved. Hence, we examined gaze and low beta electroencephalography (EEG) activity patterns when predicting the trajectory, arrival position, and arrival time of a parabolic moving target. Participants' EEG signals were recorded while they engaged in two tasks: the pursuit strategy task (PST) and the saccade strategy task (SST). In the PST, participants were instructed to visually track the target throughout its trajectory and

indicate when it reached its endpoint. Conversely, in the SST, participants were instructed to shift their gaze to the anticipated endpoint of the ball's arrival. No significant differences were observed in the position error (PE) associated with the target's arrival position between the SST and the PST, which suggests that successful prediction of the arrival position can be achieved even without employing a "strategic" pursuit approach. Notably, the SST elicited significantly higher levels of low beta EEG activity in the secondary visual cortex ($p<.05$), primary motor cortex ($p<.05$), and right posterior parietal lobe ($p<.05$) compared to the PST. This low beta EEG activity during the SST likely corresponds to visuospatial attention directed towards the moving target, tracking of the moving target, and focusing on the arrival position. Furthermore, the small PE group at response exhibited significantly higher levels of low beta EEG activity in the middle temporal (MT) visual area ($p<.05$) compared to the large PE group, suggesting that the low beta EEG activity in the MT visual area may more accurately detect the speed and direction of the moving target for individuals with a smaller PE at response. The results of this study indicate that it is unnecessary to keep an eye on the moving target and keep pursuing it. In addition, our study suggests that it is necessary to quickly detect the speed and direction of the moving target in the MT visual area and perform a saccade strategy.

Disclosures: **R. Koshizawa:** None. **K. Oki:** None. **M. Takayose:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.04/EE2

Topic: E.01. Eye Movements

Support: DFG FOR 1847

Title: Varying reward expectancies do not affect trial-by-trial amplitude learning in a random error saccadic adaptation context

Authors: *M. SHAFIEI[1], P. THIER[2];
[1]Thier Lab, Hertie Inst. for Clin. Brain Res., Tübingen, Germany; [2]Cognitive Neurol. Lab, Hertie Inst. for Clin. Brain Research, Univ. of Tübingen, Tübingen, Germany

Abstract: Previous studies have indicated that motivation reflecting reward expectancies has an impact on dynamic aspects of saccadic eye movements with higher motivation entailing shorter reaction times and larger peak velocities (Hikosaka et al., J Neurophysiol., 2006). Moreover, higher reward expectancies accelerate saccadic directional adaptation driven by retinal errors that occur in a consistent manner, although the overall magnitude of learning remains unaffected (Kojima and Soetedjo, Neurosci., 2017). Previous research has established that saccadic learning does not require error consistency as even single errors have an impact on a subsequent saccade (Junker et al., PloS Biol., 2018). More specifically, a single inward error results in a larger subsequent saccade, while an outward error entails a smaller one. We hypothesized that varying

reward expectancies might also modulate the impact of such individual errors rather than requiring the consistency prevailing in the aforementioned study of Kojima and Soetedjo. To critically test this expectation, we studied two monkeys in a paradigm in which saccadic over- and under-shoots resulted from randomly shifting the target inward or outward during a target directed saccade. We implemented directional rewards that were independent of the type of error induced. In a given block, only saccades made to either the left or right side of the display were rewarded. The direction-reward contingency was reversed from one block to the next with 8-10 blocks constituting an experimental session. Our findings from the first monkey (analysis of data from the second monkey in progress) showed that rewarded saccades exhibited significantly shorter reaction times by 50.2 ms, on average, and higher peak velocities by an average of 36.3 deg/s compared to the non-rewarded saccades. We could also replicate the findings Junker et al. (PlosBiol., 2018), showing that trial-by-trial changes in the amplitude of future saccades are a function of the past retinal errors (beta coefficient = 0.08, $p << 0.0001$). Surprisingly and in contrast to our initial hypothesis, we found that that reward did not modulate the impact of a given retinal error on the amplitude of the subsequent saccade. In a nutshell, in this first monkey reward expectancies clearly influenced the dynamic characteristics of saccades, however, without exerting a discernible influence on the extent of learning from individual past errors. Hence, an impact of reward expectancies on learning from past errors may need a certain amount of consistency over time, dispensable for the reward-dependent control of saccade dynamics.

Disclosures: **M. Shafiei:** None. **P. Thier:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.05/EE3

Topic: E.01. Eye Movements

Support: R01EY022854
R01EY024831

Title: A dynamical system model of monkey superior colliculus activity for stationary and moving targets

Authors: *F. YANG, N. GANDHI;
Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) is a laminar subcortical structure essential for converting visual inputs into motor commands for eye movement generation. The neural response to a stationary visual stimulus and the corresponding motor signal for saccade execution have been well-studied. Computational studies have advanced dynamical systems models that accurately simulate visuomotor firing rates of individual and population of neurons, while incorporating known intracollicular connectivity. In contrast, SC response to a moving target and the

interceptive saccade directed to it are understudied. We previously published that the tuning curve shifts during the motor epoch based on the direction and the speed of the target, which indicates the possibility of shifting the entire neural population on the SC or morphing the population representation. Our preliminary work indicates that, during the visual epoch, single-neuron activity may be similar for moving and stationary targets, although information about the moving target may be encoded in the latent factors. It is not known whether current models of SC can simulate neural activity associated with moving targets and interceptive saccades. Thus, we propose to start with a one-dimensional dynamical system model based on the Arai et al. (1994) architecture for visual and motor responses to a stationary target. The framework will be updated to include superficial, intermediate, and deep layers, each with its own parameters for local excitation and inhibition. Communication across layers, global inhibition from basal ganglia, and feedback from the downstream brain generator will also be considered. We will train the model with data recorded from monkeys producing saccades to stationary and moving targets as well as no-go trials associated with a moving target. Our objective is to have the same model simulate accurate sensory and saccade-related activity in individual neurons and across the SC population for both stationary and moving targets. We will also validate our model by analyzing the weights in each layer to assess whether it is consistent with local excitation and distal inhibition results reported in the previous studies.

Disclosures: **F. Yang:** None. **N. Gandhi:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.06/EE4

Topic: E.01. Eye Movements

Support: NIH EY024831

Title: Local field potential features in the primate superior colliculus during visually-guided saccades inside and outside the response field

Authors: *C. BOURRELLY, N. GANDHI, *C. BOURRELLY;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) is a central node in the neural circuit that mediates visually-guided saccades. The topographic organization of space along its rostrocaudal and mediolateral dimensions and the systematic transformation of sensation to action along its dorsoventral axis have been well characterized for spiking activity but to a lesser extent for the local field potential (LFP). Spiking activity represents the output of neurons, and the LFP signal reflects integrated activity including input signals within a volume of tissue around the recording site. We recently described visuomotor features of the LFP signal along the dorsoventral axis of SC during saccades directed in the response field (RF) of neurons encountered in the track. We

now evaluate this signal for targets and saccades away from the optimal location. Specifically, we applied current-source density (CSD) analysis to LFP signals and identified sources and sinks across the SC layers to assess functional connectivity during sensation and action epochs. Given the hypothesis that intracollicular circuitry is dominated by local excitation and distal inhibition connectivity of SC neurons, particularly in the intermediate layers, we expected to observe inhibitory signatures in the CSD signal during the movement epoch, especially between the two SC. Using multi-contact laminar electrode inserted orthogonal to the SC, we recorded spiking and LFP activities in rhesus monkeys performing a visually guided delayed saccade task. In our current datasets, the target was placed at one of 8 locations radially equidistant in direction. Using CSD analysis, we compared LFP activities during both the sensory and the motor epochs and across depth for each target location. During the sensory period, a strong sink (putatively excitation) in the CSD signal was found after the appearance of the target in the RF but not when the target was presented outside the RF. During the motor epoch, when the target was presented in the RF, strong source and sink activities were observed in the CSD signal around the time of the saccade. Interestingly, when the target was located outside the RF, we observed solely a source in the CSD signal around the time of the saccade. This source in the CSD signal for outside RF targets likely reflects an inhibitory input present in the LFP activity. This result suggests a global inhibition in the SC during the production of the saccade and supports the hypothesis that the LFP can represent the input signal. All together, these results are informative about spatial and temporal processing in the SC during saccade generation.

Disclosures: **C. Bourrelly:** None. **N. Gandhi:** None. **C. Bourrelly:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.07/EE5

Topic: D.07. Visual Sensory-Motor Processing

Title: Signaling of trans-saccadic prediction error by foveal neurons in the monkey superior colliculus

Authors: *T. ZHANG[1,2,3], A. BOGADHI[4], Z. HAFED[1,2,3];
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Abstract: The superior colliculus (SC) possesses visual machinery supporting both foveal analysis and peripheral object detection. This structure also emits movement-related discharge that is relayed to both the downstream oculomotor control network and upstream cortical areas. This places the SC in an ideal position to both control orienting responses as well as bridge periods of sensory uncertainty associated with rapid eyeball rotations. Yet, the mechanisms with which peripheral visual information may be trans-saccadically relayed to foveal SC visual

representations are not fully understood. Here we asked 2 macaque monkeys to generate 8-10 deg delayed, visually-guided saccades to peripheral grating targets, while we recorded foveal SC neurons. Intra-saccadically, we flipped the target appearance such that the foveal neurons experienced a post-saccadic image that was different from the peripheral pre-saccadic one. We tested pre- and post-saccadic images having different spatial frequencies (circular grating of 1 or 4 cycles/deg; cpd), different shapes (circle or square encompassing a grating texture that did not change intra-saccadically), or a combination of the two (both shape and texture within it changed intra-saccadically). Importantly, the foveal neurons did not respond to the peripheral stimulus onsets on their own, suggesting that the pre-saccadic images did not directly stimulate these neurons' response fields (RF's). We analyzed the post-saccadic visual reafferent responses of the foveal SC neurons with or without intra-saccadic image changes. Foveal SC visual reafferent responses were enhanced when the spatial frequency content of the saccade target image changed intra-saccadically. Shape changes only increased reafferent responses when the texture within the shape had a high spatial frequency; and, shape and frequency changes reflected the results of the previous two manipulations. These effects did not occur when we simulated saccades during fixation by rapidly translating a peripheral grating to the fovea and changing its appearance mid-flight. Our results suggest that foveal SC visual representations might receive a predictive signal about the visual appearance of the peripheral pre-saccadic target. One potential source of such a predictive signal could be the SC motor bursts themselves, which we recently found to reflect the visual appearance of the eccentric saccade target (Baumann et al., 2022).

Disclosures: **T. Zhang:** None. **A. Bogadhi:** None. **Z. Hafed:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.08/EE6

Topic: E.01. Eye Movements

Support: the National Basic Research Program of China (31871079)
Shanghai Municipal Science and Technology Major Project (2018SHZDZX05, 2021SHZDZX)

Title: The different role of the dorsolateral prefrontal cortex (dlpfc) and the lateral intraparietal cortex (lip) in the hierarchical control of learned saccade sequence

Authors: *Q. WANG, B. SHI, J. JIA, J. HU, H. LI, X. JIN, A. CHEN;
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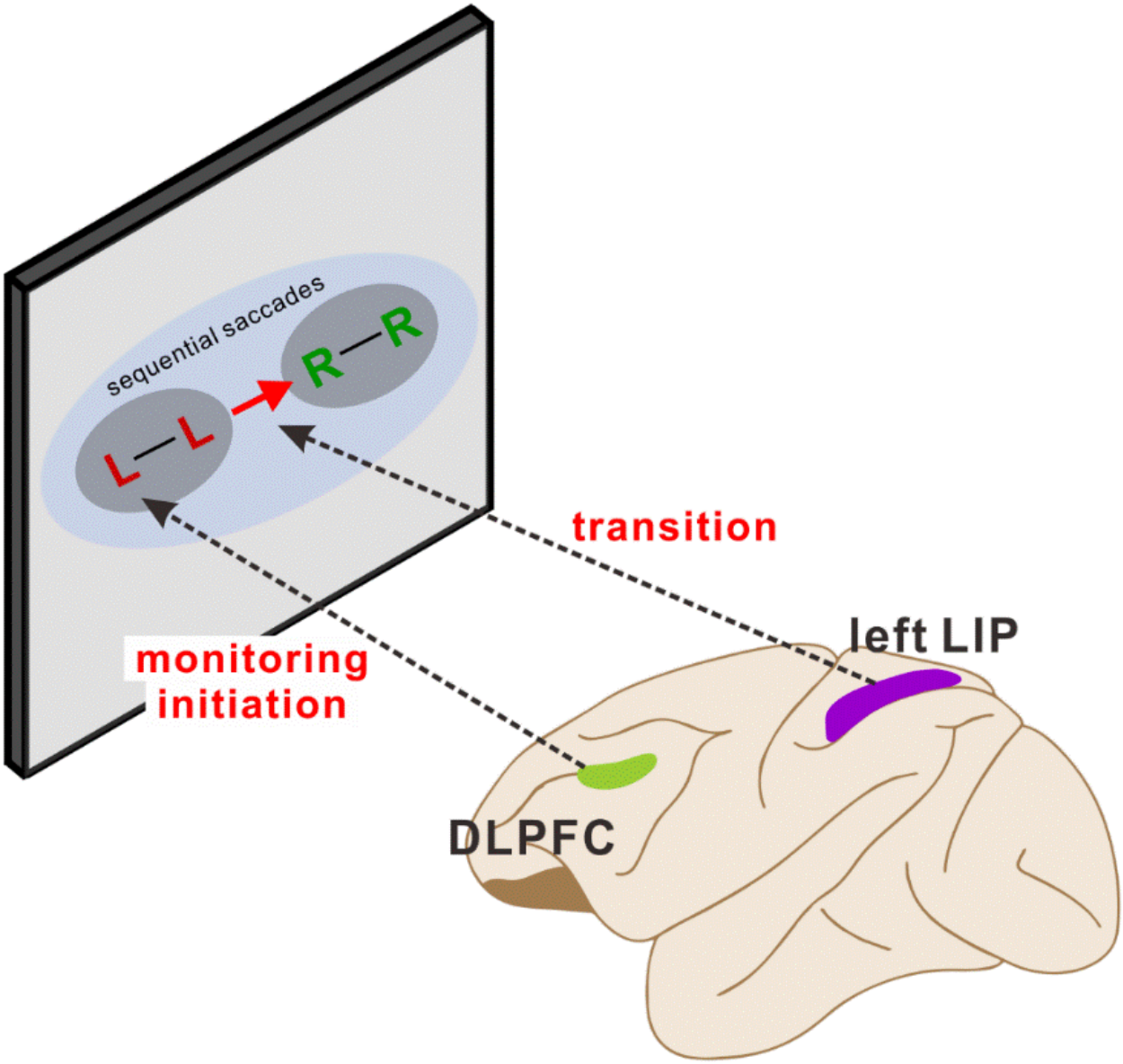
Abstract: Action sequences are suggested to be organized in a hierarchical manner in which individual actions are organized into elements, subsequences, then sequences. However, how these different levels of sequence are processed in the brain remains unknown. Here, we investigated and compared the role of the dorsolateral prefrontal cortex (DLPFC) and the lateral

intraparietal cortex (LIP) in sequence execution by training monkeys (Macaca mulatta, male, 8 ~ 12 kg) to perform a set of hierarchically organized saccade sequences (e. g. left-left-right-right and right-right-left-left). We found that inactivating DLPFC significantly increased the response latency of the first saccade at the sequence level, and the “start” signal of sequence was also observed in neuronal activities. Differently, LIP exhibited a unique feature at the subsequence level: it represented the end of the ipsilateral subsequence (e.g. left-left subsequence if the cell was recorded in left LIP), and the start of the contralateral subsequence, indicating that LIP might play a role during the subsequence transition. Further electrical microstimulation experiments on LIP significantly changed the structure of saccade sequences. Our results suggest that DLPFC might be actively involved in the sequence initiation, whereas LIP may serve as an important intermediate layer in the hierarchical motor control network for subsequence switch.



Disclosures: **Q. Wang:** None. **B. Shi:** None. **J. Jia:** None. **J. Hu:** None. **H. Li:** None. **X. Jin:** None. **A. Chen:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.09/EE7

Topic: E.01. Eye Movements

Support: Brain/MINDS grant 19dm0207093h0001
Grant-in-Aid for Scientific Research 23H03700

Title: Topographic organization of the saccade related areas in dorsal frontal cortex of common marmoset

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Abstract: Several areas in the dorsal frontal cortex (DFC) and their downstream, superior colliculus (SC), are involved in both saccade generation and cognitive functions, such as attention, in primates. In the SC, a topographic organization of saccadic control (small to large saccades controlled by rostral to caudal SC; upper to lower visual field saccades controlled by medial to lateral SC) has been well studied. However, because the upstream DFC are in the sulci in macaques and are difficult to map accurately, whether the same principle applied in those areas remains elusive. Here, we aim to use the common marmoset, with its lissencephalic cortex and human-like saccadic behavior, to investigate the saccade related areas in the DFC and their projections to the SC. We applied electrical microstimulations (biphasic current at 250 Hz for 30 trains) with tungsten electrodes in the DFC while two marmosets performing gap saccade task to identify the saccade evoking areas. We systematically varied the initial gaze locations to assess the evoked saccade types. In separate animals, we injected viral tracers with TET amplification (AAV1-Thy1S-tTA mixed with either AAV1-TRE-clover or AAV1-TRE3-Vamp2-mTFP1) into the same brain areas and analyzed their projection to the SC. All microstimulation and viral injection sites were transformed to the BMA 2019 marmoset atlas template for comparison across animals. We successfully evoked saccades in areas 45, 8aV, 8aD, 6DR, and 6Va. The evoked saccades were mainly goal-directed. Vector-based saccades could only be evoked in a small region around areas 45, 8aV and 6Va. Areas 45, 8aV, and 6Va exhibited lower evoking threshold (< 50 μA), lower evoking latency (< 60 ms), and projection to the intermediate layer of the SC, whereas 8aD and 6DR showed higher evoking threshold, higher evoking latency, and

projection to the deeper layer of the SC. Topographic projection to the SC was also observed, with area 45 to 8aV projected rostral caudally and rostral to caudal 8aV projected medial laterally to the SC. The systematic change in evoking saccade amplitude and direction in these areas was in line with the established topographic control of saccades in the SC, considering the corresponding topographic projection. Taken together, we identified the topographic organization of saccade related areas in the marmoset frontal cortex functionally using microstimulation and anatomically using viral tracing and both methods showed consistent results with the SC topography. Our results will not only help us to fill the gap in previous primate oculomotor research, but also provide guidance in identifying these areas for studying other cognitive functions.

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Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.10/EE8

Topic: E.01. Eye Movements

Support: Brain/MINDS grant 19dm0207093h0001
Grant-in-Aid for Scientific Research 23H03700

Title: The Effect of Muscimol Induced Inactivation of the Frontal Eye Field in Common Marmosets

Authors: *W. AMLY[1], C.-Y. CHEN[2], H. ONOE[4], T. ISA[3];
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Abstract: For over a century, researchers have discovered the involvement of the frontal eye field (FEF) in eye movements in macaque monkeys. Neurons within the FEF exhibit activity prior to and during saccades, and electrically stimulate the FEF have demonstrated the ability to elicit saccades. However, the fact that removing the FEF surgically has caused only minor saccade deficits made its contribution to saccade generation elusive. Only until the late nineties, a series of studies were conducted to reversibly inactivate the FEF, revealing significant impairments in saccade and smooth pursuit eye movements. These findings have once again highlighted the critical role of the FEF in the cortical control of eye movements.Our lab has been exploring the putative FEF areas in the marmosets, a new world monkey, using electrical stimulation and tracer injections. However, to conclusively determine whether these areas in marmosets truly correspond to the FEF and exhibit similar functions in the cortical control of eye movements as observed in macaque monkeys, we recognize the need for an ultimate test: the

acute reversible inactivation. Therefore, we decided to use muscimol, the $GABA_A$ agonist, to perform the experiment. To target the putative FEF, we performed MRI scan of the marmoset and designed a chamber that covered areas 45, 8aV, 8C, 8aD, 6Va, 6DR, 6DC following our stimulation results. We injected 0.5µl of 5mM muscimol (at a rate of 0.2µl/min) per injection site. One-hour post-injection, the marmoset performed the visually guided saccade tasks, and we collected its eye movement data. To ensure recovery and obtain control data, we administered muscimol every other day.Due to the lissencephalic nature of the marmoset brain, we were able to shift our inactivation location systematically within the chamber area and we observed focal saccade deficits as predicted from our stimulation results. Similar to what have been described in macaques, the marmoset exhibited a slowdown in saccade latencies, partial neglect of the contralateral hemifield, decrease in success rate, more scattered saccade starting and landing point and saccade duration prolongation after muscimol injection. Furthermore, we observed saccade overshooting on the ipsilateral side of the inactivation, likely due to disturbance in the balance of population coding in the FEF. In conclusion, our study confirms the previous micro-electrical stimulation study findings and provides evidence that marmosets possess a fully functional FEF, similar to what has been observed in macaques. Additionally, we have demonstrated the effectiveness of muscimol inactivation as a valid method for mapping the FEF in marmosets.

Disclosures: **W. Amly:** None. **C. Chen:** None. **H. Onoe:** None. **T. Isa:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.11/EE9

Topic: D.07. Visual Sensory-Motor Processing

Title: Transient focal inactivation of the primary visual cortex abolishes saccadic inhibition

Authors: *T. MALEVICH[1,2,3], Y. YU[1,2,3], M. P. BAUMANN[1,2,3], A. BUONOCORE[4], M. YOSHIDA[5], Z. M. HAFED[1,2,3];
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Abstract: Exogenous visual stimuli exert a dramatic, and inevitable, inhibitory effect on saccade generation, even before overt orienting to the stimuli is possible. This effect manifests itself as an almost complete cessation of saccade generation within <100 ms from stimulus onset, in a phenomenon known as saccadic inhibition. Although the dynamics and functional implications of saccadic inhibition have been extensively studied over two decades, the underlying neural circuits mediating such rapid sensory-driven oculomotor effect are still debated. Indeed, while current models of saccadic inhibition invoke lateral inhibitory interactions in structures like the

superior colliculus (SC) and frontal eye field (FEF), reversible inactivation of both areas did not eliminate, or even modulate the properties of, saccadic inhibition (Hafed et al., 2013; Peel et al., 2016). Here, motivated by the fact that saccadic inhibition is necessarily initiated by first sensing the presence of an exogenous stimulus, we investigated whether the primary visual cortex (V1) is necessary for this phenomenon to occur. In two macaque monkeys, we first electrically stimulated V1 with a brief microstimulation pulse train simulating a visual burst (300 Hz biphasic stimulation; 50 ms duration; ~90-100 μA). The monkeys fixated a small spot, and we either presented a visual stimulus or an electrical pulse train. We measured fixational saccades and found that they were robustly inhibited in both cases, with the inhibition starting earlier with electrical microstimulation than visual stimulation, due to the bypassing of retinal afferent signaling. Thus, V1 is sufficient for saccadic inhibition. In contrast, the same experiments in the SC (~10-30 μA) did not lead to inhibition at all, but rather to increased microsaccade likelihood. We then reversibly inactivated V1 in one monkey via muscimol. We presented stimuli in the visual field location affected by the muscimol injection or in a similar location in the other (intact) hemifield. Saccadic inhibition was completely abolished in the affected side, suggesting that V1 is necessary for inhibition. Finally, to investigate whether visual pathways other than the geniculo-striate one can still be relevant for saccadic inhibition under some circumstances, we analyzed eye movements in two blindsight monkeys having had long-lasting chronic V1 lesions. Saccadic inhibition occurred in these animals, likely due to plasticity and reinforcement of alternate pathways. Our results show that, in the intact brain, visual signals in the oculomotor system that ultimately dictate the visual feature tuning properties of saccadic inhibition must pass through V1.

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Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.12/EE10

Topic: E.01. Eye Movements

Title: Modulation of Saccadic Inhibition by Distractor Repetition during Letter Scanning

Authors: *J. A. EDELMAN, C. KYAN;
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Abstract: Real-world visuomotor behavior often occurs in the face of potentially distracting visual events. While suddenly appearing visual distractors have been shown to temporarily but dramatically hinder saccade initiation ~90 ms after their appearance, a phenomenon referred to as saccadic inhibition (SI), we hypothesized that during naturalistic tasks the saccadic system would habituate to repeated distractors, allowing the desired behavior to proceed unhindered. This study addressed this hypothesis by measuring saccadic inhibition in a letter-scanning task

with distractors presented in various spatiotemporal contexts. Eye movements were recorded using an Eyelink II eye-tracking system (SR Research) at a sampling rate of 500 Hz. Visual stimulus presentation, using a CRT monitor (85 Hz), and data collection were performed using Experiment Builder (SR Research). Participants were instructed to scan a horizontal 64-alphanumeric character array, silently count the small number (0-9) of embedded digits among the letters in the array, then indicate the number of digits seen by a key press. There were four distractor conditions: 1) no distractors, 2) square (2°) distractors appearing every 300-400 ms at different locations or, 3) at one location in a trial, and (4) two large horizontal bars spanning the visual display above and below the linear letter array. Large distractors induced a substantial amount of SI. The smaller, square distractors appearing at different locations elicited less SI, while distractors presented repeatedly at a single location resulted in minimal SI. These findings indicate that the size and positional constancy of distractors influence saccadic inhibition during a letter scanning task. Performance on the task, measured by counting accuracy, total time of scanning, and number of saccades per trial, was at most only modestly affected by distractor condition and exhibited variability across participants. These results suggest that the saccadic system can partially habituate to repeated distractor presentation, except when distractors are large in size. Moreover, even large, repeated distractors have a limited effect on the performance of naturalistic tasks that require a rapid sequence of saccadic eye movements.

Disclosures: **J.A. Edelman:** None. **C. Kyan:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.13/EE11

Topic: E.01. Eye Movements

Title: A new binocular control model (ISMYS) generates miniature eye movements of fixation

Authors: ***S. HEINEN**[1], A. CHANDNA[1], D. SINGH[1], S. N. WATAMANIUK[2,1];
[1]Smith-Kettlewell Eye Res. Inst., San Francisco, CA; [2]Psychology, Wright State Univ., Dayton, OH

Abstract: Curiously, knowledge of how smooth and saccadic fixational eye movements are controlled is lacking despite that much of visual perception occurs during fixation. This may be partially because we assume Hering's Law of oculmotor control in which the eyes are yoked and moved with identical signals. However, there is evidence that smooth movements, often referred to as "drift", undergo periods of vergence during fixation, possibly to enable fusion. To test this, we investigated ocular fixation using stimuli that varied in fusional demands, a .2 deg dot or a 6 deg diameter ring. Observers fixated the center of each stimulus in 20 sec trials. Consistent with previous literature, a fixation spot evoked significant horizontal "microvergence" where eye drift was oppositely directed. Curiously, the 6 deg ring also produced microvergence, and both stimuli produced similar proportions of vertical and horizontal microvergence. This suggests that

microvergence is the result of stochastic neural noise. In contrast, microsaccades were always conjugate, suggesting a different mechanism for their generation. We previously introduced a binocular eye movement model which incorporates independent eye control signals that interact with a unitary conjugate one (Heinen et al., SfN 2022). Here, using our ISMYS model (Independent Smooth Movements/Yoked Saccades) we test whether neural noise explains observed microvergence by adding independent white noise to each eye controller. As a result, the model generated slow microvergence in the same proportion as observed in the human data. Providing a monocular position step to the model produced conjugate microsaccades. The results suggest that microsaccades are generated by a unitary conjugate mechanism, and slow drift is generated by independent ocular control, which during simple fixation is driven by neural noise.

Disclosures: **S. Heinen:** None. **A. Chandna:** None. **D. Singh:** None. **S.N. Watamaniuk:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

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Program #/Poster #: PSTR278.14/EE12

Topic: E.01. Eye Movements

Support: NSERC Discovery Grant 2016-05296
CIHR Operating Grant 102482

Title: Target-distractor competition varies between allocentric and egocentric reference frames depending on the state of the decision-making process

Authors: *M. FALLAH, C. OLENICK, H. JORDAN;
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Abstract: Recent studies have shown that during the active perceptual decision-making process, saccade trajectories are shifted towards the distractor, but once the process is completed and the distractor is inhibited, trajectories shift away from the distractor (Kehoe, et al, 2018, 2021; Giuricich, et al, 2023). Furthermore, the magnitudes of the shifts were dependent on the distance between the target and distractor (Giuricich, et al, 2023). While saccade motor plans are encoded in egocentric reference frames, prior studies used iso-eccentric stimuli and thus could not determine if the target-distractor competition shifts in trajectories were based on egocentric or allocentric reference frames. We used a saccadic response delayed match-to-sample task where the target and distractor varied in both allocentric and egocentric distances. This allowed us to determine the reference frames underlying the target-distractor competition driving the shift in saccade trajectories. The results (38 participants: 30 female, 8 male) show that during the active decision-making process, the distance between the target and distractor in both allocentric and egocentric reference frames contributed to shifts in saccade trajectories towards the distractor. There was also a response bias for the nearer item in egocentric coordinates (shorter saccades).

In contrast, when the perceptual decision-making process was complete and the distractor was inhibited, only the distance in the allocentric reference frame contributed to trajectory shifts away from the distractor. There was no clear pattern for sex differences, although the low number of male participants limited this analysis. Therefore, saccade planning and execution depend on both perceptual processing (target-distractor discrimination) in allocentric reference frames and the competition between oculomotor plans in egocentric reference frames during active decision-making. However, when the target is identified and the distractor is inhibited, the effect of distractor inhibition on saccade trajectories is based on an allocentric reference frame, suggesting it is maintained in visual rather than oculomotor areas.

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Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.15/EE13

Topic: D.07. Visual Sensory-Motor Processing

Support: R01 63015812

Title: Effects of saccades on visual perception in mice

Authors: *A. BUTEAU, J. HUNT, A. POLEG-POLSKY, G. FELSEN;
Physiol. and Biophysics, Univ. of Colorado, Anschutz Med. Neurosci. Grad. Training Program, Aurora, CO

Abstract: Rapid orienting eye movements - saccades - are thought to cause modulation of neural activity throughout the visual hierarchy in order to stabilize representations of the visual world. Little is known about the circuit and mechanisms underlying this phenomenon. Our overall goal is to relate the circuits that govern saccadic modulation to the perceptual effects of saccades on visual behavior. We have therefore developed a mouse model to examine saccadic modulation at the levels of circuitry and perception. In this study, we focus on the effect of saccades on visual perception in wild-type mice. We hypothesized that perceptual acuity will be altered by saccades due to saccadic modulation of neuronal visual representations. To test this idea, water-restricted head-fixed mice were presented with a static grating that incremented in contrast 0% to 30% from baseline for 50 ms at pseudorandom intervals, and were trained to report the contrast change by licking a spout for a water reward. On a subset of trials, we reliably elicited saccades with an air puff to the ear. Trials occurred every 8-10 seconds, and consisted of either the contrast change, the air puff, or both, to control for potential effects of the air puff and isolate the perisaccadic effects on perception. We are currently examining whether and how perceptual thresholds for reporting the contrast change are altered by the presence of saccades. Our preliminary data suggest that saccades affect perception in mice, which will inform future investigation into the circuits mediating active vision.

Disclosures: **A. Buteau:** None. **J. Hunt:** None. **A. Poleg-Polsky:** None. **G. Felsen:** None.

Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.16/EE14

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant EY033651-01

Title: Peri-saccadic modulation of visual neurons in the mouse superior colliculus

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[1]Univ. of Colorado, Anschutz Med. Campus, Aurora, CO; [2]U. of Colorado Sch. of Med., U. of Colorado Sch. of Med., Aurora, CO; [3]Univ. of Colorado Sch. of Med., Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Animals use ballistic reorienting movements called saccades to actively explore their environment for salient visual targets. Saccades result in a transient modification of visual perception such that it becomes difficult to perceive luminance- and contrast-modulated stimuli which appear around the time of saccades, a phenomenon referred to as saccadic suppression. Saccadic suppression is associated with a decrease in responsiveness across the visual system including the midbrain superior colliculus (SC), a highly conserved visuomotor structure required for generating saccades. In primates, many studies have shown that visual responses in SC neurons are significantly attenuated around the time of saccades, but the neural circuitry which produces this neural suppression has yet to be elucidated. Ex vivo slicework in mice has identified a putative circuit for saccadic suppression in the SC which remains to be examined in vivo. To understand how saccadic suppression arises in the SC, we collected high-density in vivo extracellular recordings of single-unit activity within the superficial layers of the SC while mice made SC-dependent saccades. Headfixed mice were placed within an immersive visual arena and shown a low-contrast drifting grating stimulus to elicit the optokinetic reflex (OKR). Periodically, the contrast of the grating was briefly elevated to evoke discrete visual responses from visually-responsive SC neurons. Visual responses within the peri-saccadic epoch (-50 ms to 50 ms before and after saccades) were compared to visual responses outside of the peri-saccadic epoch. We found that visual SC neurons exhibited peri-saccadic modulation of visual responses around the time of saccades. These data are the first to demonstrate that visual neurons in the mouse SC are modulated around the time of saccades. Future work will focus on manipulating individual elements of the putative circuit for saccadic suppression in the SC using combined chemogenetics and high-density extracellular recordings.

Disclosures: **J. Hunt:** None. **G. Felsen:** None. **A. Poleg-Polsky:** None.

Poster

PSTR278. Eye Movements: Saccades

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Program #/Poster #: PSTR278.17/EE16

Topic: E.01. Eye Movements

Support: CIHR Foundation Grant MOP-FDN-148418
Parkinson Canada Graduate Student Award
Ontario Brain Institute/Government of Ontario
Canada Research Chairs Program

Title: Exploring oculomotor biomarkers for neurodegenerative disease diagnosis and features using structured and unstructured eye movement tasks

Authors: *H. C. RIEK[1], D. C. BRIEN[1], B. C. COE[1], B. J. WHITE[1], S. E. BLACK[2], M. FREEDMAN[3], A. E. LANG[4], C. MARRAS[5], M. MASELLIS[7], R. H. SWARTZ[7], C. TARTAGLIA[6], L. ZINMAN[8], D. P. MUNOZ[1];
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Abstract: Developing behavioural biomarkers for neurodegenerative disease will prove a significant advancement in their diagnosis. Due to extensive overlap between oculomotor and neurodegeneration-affected circuitry, quantifying saccade behaviour during eye movement tasks produces many objective potential biomarkers for neurodegenerative diseases. Both structured and unstructured tasks yield parameters that comprehensively characterize saccade behaviour, but understanding links between task parameters and their relationships to disease processes is crucial to use of eye movements as the foundation of future disease screening and diagnostic tools. We evaluated saccade behaviour in a large cohort of neurodegenerative disease patients from the Ontario Neurodegenerative Disease Research Initiative: 33 Alzheimer's disease (mean age 72, 19 male), 73 mild cognitive impairment (mean age 71, 41 male), 20 amyotrophic lateral sclerosis (mean age 61, 13 male), 19 behavioural variant frontotemporal dementia (mean age 68, 14 male), 9 progressive supranuclear palsy (PSP, mean age 71, 5 male), and 117 Parkinson's disease (mean age 68, 91 male), and 101 healthy age-matched controls (mean age 67, 34 male). All completed a structured task (interleaved pro- and anti-saccade task (IPAST): looking at or away from a peripheral visual stimulus according to the colour of a central fixation point) and an unstructured task (free viewing task (FV): instruction-free viewing of rapidly switching video clips). Examination of differences between disease groups in each task revealed that both can differentiate diagnoses and disease features. IPAST revealed increases in anti-saccade error rates (indicating voluntary control deficits) with cognitive impairment, and motor impairment (e.g. saccade hypometria) in movement disorders, but few limitations in fast visuomotor processing. FV revealed key disease features such as vertical gaze impairment in PSP and between-group

saccade rate differences immediately following clip change-induced visual perturbation. Inter-task correlations may illuminate shared underlying neural circuitry; preliminary results suggest parameters from early epochs following FV clip change correlate to fast visuomotor parameters from IPAST, while saccade rate in later epochs correlates to IPAST parameters measuring voluntary control. Full behavioural characterization of structured and unstructured oculomotor tasks in neurodegeneration, and links between tasks, will enable development of an objective behaviour-based clinical screening tool leveraging the breadth of oculomotor data to diagnose neurodegenerative disease.

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Poster

PSTR278. Eye Movements: Saccades

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.18/EE17

Topic: E.02. Cerebellum

Support: 1R37NS128416

Title: Saccurate: saccade curation gui for ground truth dataset construction, post curation and evaluation

Authors: J. ZANG[1], **M. FAKHARIAN**[1], P. HAGE[3], J. PI[2], A. SHOUP[1], *R. SHADMEHR[4]; [1]Johns Hopkins Univ., Baltimore, MD; [2]Johns Hopkins Univ., Ellicott City, MD; [3]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Johns Hopkins Univ. Dept. of Biomed. Engin., Baltimore, MD

Abstract: Saccades are essential for neuroscience tasks involving reward, motor function, and learning. Deep learning networks have emerged as a superior saccade detection tool, outperforming traditional thresholding methods across a wide range of saccade amplitudes. However, the field lacks reliable ground truth datasets and effective curation tools to reduce false positive errors in neural data analysis. To address this, we developed a user-friendly GUI that enables human experts to build ground truth datasets and curate results obtained from deep networks. Our approach utilizes saccade kinematics features such as acceleration to deceleration time ratio (Van et al. 1987), Q factor (Baloh et al. 1975), main sequence plot (Bahill et al. 1975), and confidence scores from the deep network itself. In our study, we recorded eye movements from three common marmosets using two video-based acquisition devices at 1000 and 2000 Hz.

We compared performance of deep networks developed by Bellet et al. (2019) with their recommended pretrained weights, networks retrained on our own datasets from different periods of the animals' lifetimes, along with the traditional thresholding methods. Results showed that the pretrained network does not generalize well to our dataset, but after retraining on curated datasets, the networks achieved around 96% accuracy and outperformed traditional thresholding methods, particularly in detecting micro saccades. Furthermore, the network demonstrated the ability to capture the variability of saccades across the animals' lifespan by incorporating training data from multiple time points. Interestingly, a network trained on data from one marmoset yielded promising results when applied to another marmoset's data, with only minor timing adjustments. In summary, we built a new tool that begins with a deep neural network to detect saccades and then allows the user to curate the results to improve accuracy. The technique is much more accurate in detecting saccades than simple threshold methods.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.01/EE18

Topic: E.04. Voluntary Movements

Support: NIH grant 5 R37 NS090610 to AJB
American Heart Association predoctoral 925 fellowship 20PRE35180131 to CR

Title: Reaching beyond the lab: virtual reality platform to study adaptation in real-world conditions

Authors: *C. ROSSI[1,2], R. VARGHESE[1,2], A. J. BASTIAN[1,2];
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Abstract: Real-world movements are characterized by many degrees of freedom and complex interactions between our body and the surrounding environment. However, traditional motor learning research has focused on simplified and highly constrained motor tasks. For example, studies of reaching movements often involve moving a single-point cursor to a target on a two-dimensional screen. While these studies provide a rigorous understanding of specific laboratory tasks, their applicability to natural movements is limited. To address this gap, we developed a platform to study reaching movements and adaptation in realistic conditions.
Participants wore a virtual reality headset (Meta Quest 2) and were immersed in a three-dimensional virtual environment that mimicked the visual landscape and sounds of a real-world garden. The task involved lifting a plate of grapes up to a bird while keeping the plate flat to prevent spillage. Crucially, participants saw their own hands in virtual reality and used both

hands to balance and lift the plate, mirroring real-life movements. Each virtual hand was represented using a 3D model with 16 bones (palm and 3 bones per finger), which tracked the position and orientation of the participant's real hand bones using cameras on the headset. The interaction between the virtual hands and plate adhered to the laws of physics (physics engine, Unity development platform), and participants had full freedom of upper limb motion.
As a proof of concept, we investigated adaptation to a gain perturbation applied to the right hand. Specifically, the position of the virtual right hand was manipulated to move slower / proportionally less than the real right hand. As expected, participants adapted by lifting the real right hand higher than the left, aligning the vertical positions of the virtual hands and keeping the plate flat. Also as expected, participants exhibited aftereffects by continuing to lift the real right hand higher after the perturbation was removed post-adaptation. These results demonstrate that adaptation of reaching movement can be induced using a task that mimics real-life conditions in important ways: unconstrained degrees of freedom, and realistic representation of hands, environment, and their interaction. This approach has the potential to enhance our understanding of real-world motor control and learning, facilitating the translation of research findings to rehabilitation interventions.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR279.02/EE19

Topic: E.04. Voluntary Movements

Support: NIH T32 HD007414 to AJB
NIH R35 NS122266 to AJB

Title: Childhood development of reinforcement motor learning under probabilistic and deterministic rewards

Authors: *N. M. HILL[1,2], L. A. MALONE[1,2], H. M. TRIPP[1,2], D. M. WOLPERT[3], A. J. BASTIAN[1,2];
[1]Kennedy Krieger Inst., Baltimore, MD; [2]Johns Hopkins Univ., Baltimore, MD; [3]Columbia Univ., New York, NY

Abstract: Motor abilities develop over the course of childhood. In the cognitive domain, learning by reinforcement develops with age; however, less is known about how children acquire the ability to use reinforcement to guide motor learning. We designed computer-based motor learning tasks to collect data remotely from participants at home to investigate how age affects children’s ability to incorporate a binary reward signal (success or failure) to modify motor behavior. Participants used a mouse, trackpad, or touchscreen to move an onscreen cartoon penguin. We created four paradigms by varying two task factors: 1) target type (continuous vs.

discrete) and 2) reward feedback (probabilistic vs. deterministic). In the continuous conditions, participants could choose to move the penguin to any location on a continuous horizontal target. In the discrete conditions participants could move to one of seven targets spread horizontally. For probabilistic feedback, the reward was determined by an unseen position-based probability gradient with a small 100% reward zone away from which reward probabilities decreased linearly to a baseline. For deterministic feedback, reward was always given within a reward zone but not elsewhere. In the key learning block, participants repeatedly reached and received binary reward. This was followed by two "clamped" feedback blocks where reward did not depend on the movement. In the first of these blocks all reaches were rewarded and in the second no reaches were rewarded. We first sampled a cohort of 93 children (age three to 17 years old) and 33 adults (age 18 to 35 years old) using the continuous target and probabilistic reward task. Over 60% of participants age nine and older learned the reward landscape and consistently moved within the 100% reward zone by the end of the learning block. In contrast, only 14% of three to eight year olds learned in this task structure. These results point to an age-related component in the ability to learn from probabilistic binary reward. Increased exploration after failure relative to after success (in the clamp blocks) predicted better overall learning performance. We sampled three additional 40 participant cohorts of three to eight year olds on the other three tasks. With discrete targets and a probabilistic reward structure, 43% of participants learned. Removing the probability gradient increased the portion of the cohort that learned to 66% (continuous target) and 88% (discrete targets). While type of target and reward structure have a combined effect on learning, a probabilistic reward structure is the biggest inhibitor to learning in young children.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

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Topic: E.04. Voluntary Movements

Support: NSERC Grant RGPIN-2019-05944

Title: Temporal credit assignment in reward-based motor learning

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Abstract: In reward-based motor learning, the movement to be learned often consists of a series of sequential steps with feedback related to the performance only arriving after all steps have

been completed. Learning under such conditions involves determining the contribution of each step to the final reward received. How humans solve this temporal credit assignment problem in the context of motor learning remains largely unknown. Here we tested human participants' capacity to solve this problem during a hand path learning task. In each trial, participants drew a top-down path crossing 4 horizontal bars, which visually divided the task into 4 steps. A single score was given at the end of the trial based on the distance between the location where the cursor crossed each bar and a preset "target" location on each bar (unknown to the participants), and the participants' goal was to maximize the score. The cursor could only cross each bar through a specific region which was colored green. The whole first bar was green, while for the next 3 bars, the green region (40% of the bar) would appear centered on the direction of the cursor's displacement vector from the previous step. This constraint on possible paths created a dependency chain between successive steps. Participants were randomly assigned to one of two groups in which the final score depended on all 4 steps equally weighted (Group 1: N = 13) or based on the last step alone (Group 2: N = 14). Participants were not informed about the weighting of the steps. Participants completed 200 trials divided into 4 blocks (50 trials each). We found that, in both groups, most participants improved their scores. In the final block, both the average score and the average absolute error in the last step were similar between Groups 1 and 2. During earlier trials, participants explored paths with little curvature. However, as trials progressed, path curvature increased in Group 1, in which the optimal path was curved, but not in Group 2, in which a maximum score could be obtained with a straight path. In Group 1, 8 out of the 13 participants obtained an average score, in the final block, that was greater than the highest possible score with a straight path. We also calculated the correlation between crossing locations in step 1 and step 4 across trials in the final block. The correlation was lower in Group 1 than in Group 2, indicating that the control of crossing locations for different steps was more independent in Group 1. Together, our results show that participants were able to shape their movement steps separately based on the overall performance score. We show that this learning process can be modeled by the Monte Carlo method with forgetting.

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Poster

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Topic: E.04. Voluntary Movements

Support: NIH Grant F32-NS122921
Princeton Blair-Pyne Fund

Title: Improvement in cognitive strategy-based performance during a visuomotor adaptation task

Authors: *O. A. KIM, J. A. TAYLOR;
Princeton Univ., Princeton, NJ

Abstract: We leverage cognitive strategies to enhance our motor performance. For instance, golfers can deliberately re-aim a shot to account for a crosswind, or they can try to recall and replicate a past swing. These kinds of strategies are also observed in the laboratory during visuomotor adaptation tasks (VMR). Participants readily re-aim to counteract a visuomotor rotation, investing processing time to flexibly discover the solution (algorithmic strategy). Participants can also cache solutions to previously-solved mental rotations in memory, allowing them to respond quickly without investing additional cognitive resources (retrieval strategy). While we know that both strategies are available, we do not know the extent to which each contributes to skill. Early on, algorithmic strategies dominate performance at the cost of increased preparation time. With training, preparation times gradually decrease without impacting performance - a classic marker of skill and automaticity. Building on prior work, we suggest two possible routes for skill refinement: improvements in spatial cognition may accelerate the execution of algorithmic strategies, or rapid retrieval strategies may replace algorithmic strategies. Here, we assessed the extent to which these two pathways to automaticity proceed with training during a VMR task. Participants conducted a center-out reaching task (visual feedback delayed to maximize cognitive strategy use). During training, they countered 20° and 60° rotations (clockwise and counterclockwise) at four target locations. With practice, the rotation size/preparation time slope decreased but remained above zero. Thus, participants improved their algorithmic strategies rather than using retrieval strategies, which would have resulted in equal preparation time regardless of rotation size. In a subsequent test phase, participants encountered new rotations (40° and 80°) in either trained or novel locations. Preparation times on trials with new rotations were consistent with the algorithmic strategy processing rate inferred from the trained rotations (2 ms/°), regardless of target location. This is in line with a general improvement in algorithmic strategies, as opposed to improvements exclusively for the practiced rotations. Altogether, we illustrate that a generalizable spatial cognitive process underlying algorithmic strategies executes more automatically with practice, although retrieval strategies may develop under different conditions. Nonetheless, these data suggest that training that improves the automaticity of algorithmic strategies may be a powerful tool for training broadly applicable motor skills.

Disclosures: O.A. Kim: None. **J.A. Taylor:** None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.05/EE22

Topic: E.04. Voluntary Movements

Title: Motion-dependent motor learning based on explicit visual feedback demonstrates no anterograde interference to learning from physical perturbations

Authors: *W. ZHOU[1], K. D. FERNANDEZ[1], W. M. JOINER[2];
[1]Univ. of California Davis, Davis, CA; [2]Dept. of Neurobiology, Physiol. and Behavior, Univ. of California, Davis, Davis, CA

Abstract: The adaptation of arm reaching movements in response to physical perturbations, such as a velocity-dependent force-field (vFF), demonstrates anterograde interference - initial learning of Task A reduces the rate of subsequently learning Task B, usually the opposite perturbation. In our recent study, we investigated the ability of subjects to learn motion state-dependent modifications to motor output based on explicit visual feedback (eVF). Specifically, subjects were provided with visual information indicating the extent to which their applied temporal force pattern matched the required velocity-dependent force profile that would have been generated under the vFF perturbation. Here, we examined anterograde interference based on eVF, as compared to the interference caused by physical vFF perturbations. Two groups of subjects were recruited to participate in two separate experiments, both employing the same paradigms but involving different forms of information for motor recalibration. All participants performed 10 cm reaching arm movements between two targets using a robotic manipulandum. The experimental protocol consisted of a training block with perturbation A, and another training block with perturbation B. In the FF group, physical vFF perturbations were experienced during the perturbation A block, followed by the opposite physical vFF perturbations during the perturbation B block. In the EVF group, eVF of the required force-velocity relationship was provided during the perturbation A block, while the opposite physical vFF force-field was applied during the perturbation B block. In the latter group, during eVF perturbation trials, subjects performed movements within force channels, and visual feedback was given on the lateral force exerted during the movement, as well as the required force pattern based on the movement velocity. We compared the learning rates for perturbation A and B between the two groups. Our preliminary results (N = 9 for both groups) revealed that learning based on physical vFF demonstrated anterograde interference on the learning of the opposite vFF perturbation (exponential growth rate was reduced from r^{A}_{FF} =0.16±0.018 to r^{B}_{FF} =0.080±0.012), consistent with previous research findings. However, learning based on eVF did not exhibit anterograde interference on the learning (exponential growth rate r^{A}_{EVF} =0.16±0.043 was similar to initial learning, $r_{FF}{}^{A}$). These findings suggest that anterograde interference in the adaptation to physical perturbations may primarily result from motor recalibrations that utilize the same learning mechanisms.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.06/EE23

Topic: E.04. Voluntary Movements

Title: Reduced visual feedback shifts the representation of visuomotor memory from extrinsic to intrinsic

Authors: *S. GURGONE, T. IKEGAMI;
Ctr. for Information and Neural Networks, Natl. Inst. of Information and Communications Technol., Osaka, Japan

Abstract: Motor learning behaviors such as stability, variability, and generalization are affected by how motor feedback is provided. The feedback-dependent learning mechanism is, however, poorly understood. Many studies have utilized three types of feedback, continuous, terminal, and binary, and examined its effect on motor learning using reaching tasks under a novel visuomotor transformation. The visual feedback of the cursor as a proxy for hand position is provided throughout the movement for continuous feedback and only at the end of the movement for terminal feedback. For binary feedback, the cursor is not visible and the success or failure of the task is provided. Previous studies have considered that different contribution of learning algorithms determines feedback-dependent learning. Continuous and binary feedback mainly involve error-based and reinforcement learning, respectively. Endpoint feedback involves both. However, differences in sensory information in feedback may also engage different learning processes. As visual information decreases from continuous to terminal to binary, the coordinate frame representing motor memory may change from the vision-based extrinsic (xy) coordinate to the proprioception-based intrinsic (joint) coordinate. To test this possibility, we examined a visuomotor adaptation of reaching with the three feedback. Three groups of participants, continuous (n=10), terminal (n=9), and binary (n=8), adapted to a gradually increased visuomotor rotation while reaching a training target. After the adaptation, we tested generalization with three untrained targets. The first was *extrinsically consistent* with the training target such that the identical hand motion led to the perfect generalization (E-C). The second was *intrinsically consistent* with the training target such that the identical joint rotation led to the perfect generalization (I-C). The third was *intrinsically inconsistent* with the training target such that the identical joint rotation leads to a zero-generalization (I-I). The generalization in the binary group was higher for the I-C target and lower for the E-C and I-I targets than the continuous group, and the terminal group was in between the two. A model analysis showed significantly different contributions of extrinsically and intrinsically represented motor memories between the groups. These suggest that reduced visual feedback shifts the motor representation from extrinsic to intrinsic. More visual feedback (continuous) may develop more extrinsic memory through error-based learning, while less visual feedback (binary) may develop more intrinsic memory through reinforcement learning.

Disclosures: S. Gurgone: None. **T. Ikegami:** None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

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Program #/Poster #: PSTR279.07/EE24

Topic: E.04. Voluntary Movements

Support: Internal Research Funds of the German Sport University Cologne, grant agreement number L-11-10011-233-150000

Title: Spatial generalization and intermanual transfer of visuomotor adaptation in virtual reality

Authors: *S. WERNER, J. GERKEN;
German Sport Univ., Cologne, Germany

Abstract: Previous research showed greater spatial generalization of learning after adaptation to prism goggles than after adaptation to visuomotor rotations in computer-generated settings. One possible explanation for this is that looking at one's own hand during prism adaptation causes the error to be more strongly attributed to one's own movement than when seeing only a representative cursor. To confirm this hypothesis we compared, for the first time in a single experimental setup in virtual reality (VR), visuomotor adaptation when looking at one's own (virtual) hand and when looking at a representative cursor. Two groups of 15 participants each (H, C) wearing VR goggles performed centre-out reaching movements to virtual target spheres with their right arm. They received visual feedback about their movement by seeing either a virtual hand (H) or a cursor (C). This feedback was veridical at baseline. In a subsequent adaptation block, the feedback was rotated 40° counterclockwise around the central starting sphere. After adaptation, spatial generalization to untrained targets, intermanual transfer to the left arm and aftereffects were measured without visual feedback. In addition, a questionnaire was used to determine the sense of agency in both experimental groups. The analysis of the questionnaire data reveals a greater sense of agency in H than in C and the analysis of variance of participants reaching errors shows faster adaptation in H than in C. Thus, our results imply that the speed of adaptation indeed depends on attributing prediction errors to internal causes. Furthermore, Student's t-tests reveal no group differences in spatial generalization, intermanual transfer, or aftereffects. However, the reaching errors in these post-tests without visual feedback were highly variable. We therefore explain the lack of difference in generalization of learning by methodological aspects of adaptation measurement in VR. Our findings are discussed with reference to different mechanisms that encompass visuomotor plasticity.

Disclosures: S. Werner: None. **J. Gerken:** None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

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Topic: E.04. Voluntary Movements

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Title: Role of Redundancy in Exploring to Learn New Coordinative Patterns in a Novel Task

Authors: *J. THOMAS, J. SMITH, R. M. BONGERS;
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Abstract: Learning the coordination of Degrees of freedom (DoF) requires the neuromotor system to explore different coordinative patterns. These patterns are temporary organization of DoFs into task specific units to achieve goal directed tasks. In the current exploratory study, we identify muscle activation patterns as DoFs. We characterize DoFs with respect to the unique size and location they occupy in the DoF space, which contains different DoF combinations during a task. The DoFs covary in a successful task to form solution within the DoF space. Learning can be strategised as exploring solutions by Central Nervous System (CNS) in the wider DoF space and within the solution space, by systematically employing DoFs over time. Moreover, the neuromotor system is redundant in that it has more DoF than necessary to perform a task, thus the CNS identifies the task relevant and task irrelevant DoFs through exploration. It is crucial to understand the exploratory behaviour of redundant DoFs to learn a novel task. Therefore, in this study we design a task to map muscle activity in isometric force production task to an object on a screen. We recruit right-handed participants to perform a continuous isometric task, whereby the muscle activation patterns in the left arm were recorded by Electromyographic (EMG) sensors. The muscle activity from groups of flexors and extensors was mapped onto a 1-dimensional spherical virtual avatar. The task was divided into 2 DoF (Low Redundancy) and 4 DoF (High Redundancy) conditions, whereby the participants had to control the position of this avatar through isometric contractions, to move it through virtual circular targets approaching towards it. Learning the mapping to navigate the avatar successfully into the targets would require the participants to explore new coordinative patterns. Results showed 40% and 10% success rate in 4 DoF and 2 DoF condition respectively, in the early phase of learning. In the late phase of learning, success rate of 10% and 5% in 2 DoF and 4 DoF respectively was observed. This may be attributed to the onset of fatigue in the late phase of learning. Results at the level of DoF indicated an increase muscle activity of all the muscles in the early phase of learning. Whereas an increase in only the agonists involved in mapping with a simultaneous decrease in activity of the other muscles that are not involved in the mapping, was observed in the late phase of learning. These findings suggest that exploration may have occurred, to converge onto a stable solution. This is in agreement with our hypothesis that learning exhibits co-activation of both agonist and antagonist pair earlier and reciprocal activation of muscles at later during the task.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

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Program #/Poster #: PSTR279.09/EE26

Topic: E.04. Voluntary Movements

Support: NIH R35 NS122266

Title: Adapting to errors in an unconstrained bimanual context

Authors: *R. VARGHESE[1], C. ROSSI[2], A. J. BASTIAN[3];
[1]Neurosci., Johns Hopkins Med. Institutions, Baltimore, MD; [2]Johns Hopkins Univ., BALTIMORE, MD; [3]KKI & Johns Hopkins, Baltimore, MD

Abstract: Many of the tasks we perform in our daily lives require the coordinated use of both hands. The purpose of this study is to better understand how people learn bimanual movements from errors that are distributed across the two arms. We forego traditional laboratory methods for a realistic 3D task that captures the complex interactions between the hands and environment, presented through a virtual reality headset (Meta Quest 2, Facebook Reality Labs). Participants were required to lift a (virtual) plate of grapes up to a perch to "feed the bird", using a virtual representation of their own hands tracked using the Leap motion controller camera (Leap Motion Inc.) mounted on the front of the headset. The motion of the arm and hand were fully unconstrained, and the visual interaction between the hands and the plate followed the natural laws of physics. We studied error-based adaptation to a visuomotor gain perturbation applied to the right hand, such that the virtual right hand appeared to move proportionally less than the true hand. Over a course of 260 trials, participants first learn to adapt to a gradually decreasing visuomotor gain by reaching higher with their true right hand and then deadapt in an abruptly introduced washout period. In addition to the online visual feedback of their arm and hand, participants also received a binary audiovisual reward feedback (trials were successful if the plate laid entirely in a rectangular target zone around the perch). In experiment 1, we compared adaptation of unimanual versus bimanual movements using our task: the unimanual group lifted the plate using the right hand alone (n = 21) and the bimanual group lifted the plate using both hands together (only the right hand was perturbed, matching the unimanual group; n = 22). We found that both groups adapted to a similar extent, but aftereffects were smaller and decayed more rapidly in the bimanual group. In experiment 2, we tested whether right hand aftereffects would be further reduced if the left hand can contribute to error correction. We doubled the size of the target zone from experiment 1. Consistent with our expectation, we found that when the target zone was wider, right-hand aftereffects were smaller and decayed at a similar rate as the bimanual group in experiment 1. There was faster deadaptation in the bimanual context suggesting that errors from both hands are integrated to estimate the position of the right hand. Understanding how the brain learns from errors in the bimanual movement context has ecological value and might be important for the design of error augmentation techniques and bimanual exercises.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

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Topic: E.04. Voluntary Movements

Support: Schweppe Scholar Award
Sloan Research Fellowship

Title: Repetition-based Motor Skill Learning is Preserved with Age

Authors: *Y. HAN[1,2,3], S. KORDE[1], A. OWUSU-OFORI[1,2], B. LIAN[1], J. SAMBANGI[1], M. DIASAMIDZE[1], L. M. WONG[1], E. J. HWANG[1];
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Abstract: The biological aging process leads to impairments in both cognitive and motor function. While the impacts of aging on cognitive function have been well-documented, its effects on motor function decline remains unclear. Existing literature suggests that aging influences motor learning in a task-specific manner: older adults may perform on par with younger adults in certain tasks after learning, while performance disparities widen in others. To further elucidate this task-specific relationship, we investigated motor learning in mice across 4 different age groups (ranging from 3 to 22 months old; N=81; female and male) performing a novel stimulus-response association task. In this task, mice learn to maneuver a visual stimulus (a Gabor patch) to the center of the screen by turning a wheel leftward or rightward. When a Gabor patch appeared on the left of the screen, moving it to the center via a rightward wheel turn constituted a correct response, and vice versa. A correct response was reinforced with a water drop reward. We analyzed their motor function attributes including reaction time, peak velocity, and trial-to-trial movements correlations over 40 training sessions. Our data revealed that older mice exhibited the longest reaction and slowest peak velocities during early training sessions. However, despite this disadvantaged performance, older mice demonstrated unexpectedly rapid learning rates in these two attributes, thus offsetting the performance disparities. By the conclusion of the training period, no motor function attributes significantly differ between younger and older mice. The trial-to-trial movement correlation that measures the consistency of motor execution improved at a similar rate regardless of age. Our results suggest that although aging impairs the motor performance of older mice, it does not degrade their learning capacities. Thus, with training, older mice improved their motor performance to a comparable level to younger mice. This finding is in stark contrast to the finding that older mice were significantly impaired in cognitive functions (i.e., correct choice rate) in the same task. In summary, our results indicate no significant differences in motor performance between younger and older mice after extensive training in this specific task, underpinned by the preservation of motor learning ability in older mice. This highlights the potential for continued learning and adaptation for the elderly, thereby offering valuable insights for interventions aimed at mitigating age-related motor function decline.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.11/EE28

Topic: E.04. Voluntary Movements

Title: Changes in muscle activation patterns during learning a new motor task

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Abstract: Learning a new motor task implies learning a new coordination pattern among muscles. The current study examined how new coordination patterns emerge. The human neuromotor system is redundant and therefore there are multiple coordinative patterns that lead to successful task performance. Hence, this implies that when learning a new task the first step is to find coordination pattern fit to perform the task. The second step is to change this coordination pattern to a preferred coordination pattern. Stated otherwise, learning might be seen as search through coordination patterns of involved muscles. This exploratory study aimed to characterise this search process. In the experiment, EMG signals of muscles in the arm are mapped onto movements of a cursor on the screen to play a virtual game in which the cursor has to follow a path. We asked, 1) whether participants improved in the task performance, and 2) does the co-variation between muscles change during learning. Until now we collected the data of five right-handed participants (mean (std) age was 22.6y (1.7), 4 females and 1 male), who had no deficits in their neuromotor system. EMG of the Extensor Carpi Ulnaris (ECU), Extensor Carpi Radialis (ECR), Flexor Carpi Radialis (FCR) and Flexor Carpi Ulnaris (FCU) of the left arm was measured with a Delsys Trigno system at 1000Hz. Participants wore a wrist brace so that they could produce isometric contractions. For each EMG signal, the control signal of the game was computed using a RMS filter over the preceding 750ms for each data point. The game showed platforms oriented in different direction that became smaller during game progression. Using the control signals, a ball had to be steered over the platforms, while staying on them, to collect boxes by hitting those with the ball. The ball was controlled using a direct mapping between the control signal and ball position where ECR moved the ball UpLeft, ECU moved the ball UpRight, FCU moved the ball DownRight and FCR moved the ball DownLeft. Participants performed three sessions of 20 mins on consecutive days. Each session started with placing the EMG sensors and calibrating the system by making pre-defined movements. In each session participant started with the widest platform. When all boxes were collected the platform became smaller, indicating the next level. Preliminary results showed that all participants learned the task and completed more levels over the different sessions (Session 1: 1-6 levels and Session 3, 4-8 levels). Over training, muscles were more independently controlled for diagonal movement directions of the ball, whereas co-variation between muscles increased for horizontal and vertical ball directions.

Disclosures: R. Bongers: None. **M. Kristoffersen:** None. **I. Slooter:** None. **V. Schuurmans:** None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR279.12/FF1

Topic: E.04. Voluntary Movements

Support: CIHR Grant MOP126158
CFI Grant 35559
NSERC Grant RGPIN-2017-04684

Title: Reconfigurations of cortical manifold structure during reward-based motor learning

Authors: *Q. NICK, D. GALE, C. ARESHENKOFF, A. DE BROUWER, J. Y. NASHED, J. D. WAMMES, R. FLANAGAN, J. SMALLWOOD, J. P. GALLIVAN;
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Abstract: Adaptive motor behavior depends on the coordinated activity of multiple neural systems distributed across cortex and subcortex. While the role of sensorimotor cortex in motor learning has been well-established, how higher-order brain systems interact with sensorimotor cortex to guide learning is less well understood. Using functional MRI, we examined human brain activity during a reward-based motor task where subjects learned to shape their hand trajectories through reinforcement feedback. We projected patterns of cortical and subcortical functional connectivity onto a low-dimensional manifold space and examined how regions expanded and contracted along the manifold during learning. During early learning, we found that several sensorimotor areas in the Dorsal Attention Network exhibited increased covariance with areas of the salience/ventral attention network and reduced covariance with areas of the default mode network (DMN). During late learning, these effects reversed, with sensorimotor areas now exhibiting increased covariance with DMN areas. However, areas in posteromedial cortex showed the opposite pattern across learning phases, with its connectivity suggesting a role in shifting from exploratory to exploitative modes of behavior. Our results identify the neural changes supporting reward-based learning, and indicate distinct transitions in the coupling of sensorimotor to transmodal cortex when refining behavior over time.
Our study sheds light on the coordination of multiple distributed neural systems during reward-based motor learning. Using functional MRI, we investigated the brain activity of human participants as they learned to shape their hand movements based on reward feedback, focusing on how different brain regions and networks interacted during the learning process. We found that when participants were uncertain about how to adjust their movements, regions of the dorsal attention and default mode networks segregated from one another; yet the same systems became integrated later, once the appropriate motor commands were acquired. Our findings suggest that changes in interactions between sensorimotor and transmodal networks enable the shift from exploratory to exploitative modes of behavior over time.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.13/FF2

Topic: E.04. Voluntary Movements

Support: CIHR grant PJT-166014
UNIQUE-IVADO Postdoctoral fellowship

Title: Dorsal premotor cortical activity reflects deliberation about reaching choices even during the initial learning of a decision-making task

Authors: *T. PEEL, P. CISEK;
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Abstract: Previous neurophysiological studies have suggested that decisions about actions involve a competition unfolding within the same sensorimotor regions involved in executing those actions. However, those observations were made in highly trained monkeys, raising the question of whether they only apply when behavior has become largely automatic or whether similar results would be found when an animal learns a novel task for the first time. Here, we investigated this question by recording neural activity in dorsal premotor cortex (PMd) while a monkey was being trained to perform a reach decision task (the "tokens task"). We used chronically implanted GrayMatter micro-drives to record individual task-related neurons and local field potentials (LFPs) over many weeks. In phase 1 of training, two target circles appeared and then, ~1s later, 15 small tokens jumped from the center into one of the targets, indicating it as the correct target to reach after a subsequent GO signal. It took the monkey about 78 trials to understand this rule. Coinciding with his moment of understanding, PMd activity responded less to target appearance, and began to instead respond to the token jump event, predicting the monkey's decision. In phase 2, tokens were randomly distributed to both targets, and the one that received the majority was rewarded. As the monkey learned this "more-is-better" rule, PMd activity reflected not just the choice, but also the level of evidence (difference in the number of tokens) on which the choice was based. In phase 3, the GO signal appeared before the token jumps, so the monkey could make his choice immediately. He was initially confused by this, and PMd activity no longer reflected the token evidence. However, after about 50 choices he became proficient again in applying the more-is-better rule, which was accompanied by the re-appearance of evidence scaling in PMd. Finally, in phase 4, the tokens began jumping one-by-one every 100ms. Already in the first days of training, PMd activity reflected the time-course of the changing evidence. For example, in "misleading" trials where the first 3 tokens jumped to the incorrect target, PMd activity was initially biased towards the incorrect target but later switched before movement onset in correct trials. Taken together, these results are consistent with a continuous flow of sensory evidence to bias action competition in PMd, suggesting that it is involved in action selection even when monkeys are learning a new task for the first time.

Disclosures: **T. Peel:** None. **P. Cisek:** None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

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Topic: E.04. Voluntary Movements

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NIH BRAIN (NIMH) 1F32MH118714
NIH NINDS R00NS114194
NIH BRAIN (NINDS) 1U19NS104649
Simons-Emory International Consortium on Motor Control

Title: Learning reaches to covert spatial targets in the corticostriatal forelimb circuitry

Authors: *A. C. MOSBERGER[1], L. J. SIBENER[1], T. X. CHEN[1], H. F. M. RODRIGUES[2], R. HORMIGO[1], J. N. INGRAM[1], V. R. ATHALYE[1], T. TABACHNIK[1], D. PETERKA[1], D. M. WOLPERT[1], J. M. MURRAY[3], R. M. COSTA[2];
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Abstract: To learn novel actions, the brain assigns credit to the movement that led to reward and refines it through practice. Often different movement strategies can lead to reward, and the aspects of movements that are initially explored may determine what is learned. We developed a spatial target task for head-fixed mice to study the refinement of different aspects of a reaching movement, and probe the content of what is learned. Mice produce complex forelimb trajectories with a 2D joystick as they learn to move it from a set start position to a hidden target area. As animals learn, credit may be assigned to the correct initial reach direction, or the or the limb position at target entry. At first, target reaches (hits) are variable in their initial direction, tortuosity, and spatial directionality measured by vector field analysis. With learning, the hits are refined in all these movement aspects. To dissociate what has been learned, we relocate the start position in probe trials while maintaining the target position, testing if animals learned to move in a specific direction or to a specific endpoint. We find that some animals move in the learned initial direction from new starts (direction learners), while other animals guide the joystick into the target by adjusting their direction (endpoint learners). This suggests that different movement aspects were reinforced in individual animals, resulting in different reach strategies. The degree to which an animal showed direction vs endpoint learning correlated with their spatial directional variability early in training, indicating that exploration affects what was learned. Lesioning the

sensorimotor cortex impaired this spatial directional variability, pointing to a role for cortex in the generation of variable movements that are thought to be reinforced in striatum. But how are different aspects of the movement encoded in the corticostriatal circuitry, i.e., corticospinal neurons (CSpn) with striatal collaterals and intratelencephalic corticostriatal (IT-CStr) neurons? Using 2-photon calcium imaging and linear decoding, we found that an ongoing hand position command is conveyed particularly by CSpns. We are now using manipulations and ablations to investigate if selective disruption of this position command affects the degree of endpoint learning. Additionally, we found that an initial direction command is conveyed by thalamus to striatum and lesioning this area distinctly impairs the refinement of the initial movement direction but does not impair spatial directional variability, suggesting that different aspects of the spatial target reach is controlled by distinct sub-circuits of the forelimb motor system.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.15/FF4

Topic: E.04. Voluntary Movements

Title: Concurrent corticostriatal dynamics across multiple cell types underlying trial and error motor learning

Authors: *M. A. NICHOLAS[1,2], E. A. YTTRI[1,2];
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Abstract: The performance of skilled motor actions is not instinctual; rather, it is learned through trial and error. While trial and error learning is crucial for survival, we still do not possess a mechanistic understanding of how the multiple motoric brain areas and cell types work together to facilitate this learning. We have proposed a functional model of motor performance in which pyramidal tract (PT) and intratelencephalic (IT) neurons of motor cortex (M1) dictate motor commands, while the direct and indirect spiny projection neurons (dSPN, iSPN respectively) of the dorsal striatum regulate the performance kinematics of those plans. To study how the brain can update motor commands, we trained mice to perform a goal-directed reach to target task and randomly changed the target bounds on a subset of blocks.
We found that mice (of both sexes) were able to learn multiple new target bounds based only on trial outcome and neural activity varied based on target location and error types. While phototagging multiple cell types and recording across M1 and striatum concurrently, we found that after changing the target bounds, neural activity on trials following errors increase more than

after rewards, specifically in the SPNs of the striatum. PT and IT neurons were less sensitive to errors but differentially modulated their activity after learning and the updating of performance after a change in target. This work suggests that following a target change, SPN activity may search out new performance policies to shape a relatively static motor command from M1 - pointing to a tiered learning approach that is delegated across different brain areas.

Disclosures: M.A. Nicholas: None. **E.A. Yttri:** None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.16/FF5

Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant RGPIN-2017-04684
NSERC PGS-D Graduate Award

Title: The structural and functional neural architectures of implicit and explicit motor learning.

Authors: *C. N. ARESHENKOFF[1], A. J. DE BROUWER[3], D. GALE[2], J. Y. NASHED[1], J. FLANAGAN[1], J. P. GALLIVAN[1];
[1]Ctr. for Neurosci. Studies, [2]Queens Univ., Kingston, ON, Canada; [3]Ophthalmology & Visual Sci., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The ability of the central nervous system to learn new mappings between motor commands and sensory feedback is critical for adaptive behaviour. Substantial evidence indicates that such learning is supported by two distinct, parallel processes: a non-conscious (implicit) process that adapts gradually through the updating of an internal forward model, and a strategic (explicit) process which is believed to be highly cognitive, and to be supported by prefrontal cortex. This latter, explicit process has been linked to executive functions, such as working memory processes, although relatively little research has attempted to systematically investigate its neural substrates.
Using functional MRI, we studied motor learning in two distinct tasks -- in the same human subjects (N = 36) -- providing different forms of feedback: A visuomotor rotation task (VMR) in which subjects learned through sensory errors, and a reinforcement-based motor learning task presenting only score feedback. By querying subjects' conscious knowledge of the rotation during VMR task performance, we identified gradients of cortical, cerebellar, and striatal functional connectivity with the motor cortex associated with subjects' explicit knowledge, as well as with their implicit adaptation. We then found that the expression of the explicit, but not implicit, gradient during the separate reinforcement-based task predicted learning in the same subjects.
While the implicit gradient agreed with a large literature characterizing the circuitry supporting the sensory-guided control of movement (including regions of the motor cerebellum, as well as

premotor and posterior parietal cortices), the explicit gradient was supported largely by regions of the default mode network. By comparing these gradients to existing cortical gradients in the published literature, we found that these two connectivity gradients could be singly explained as opposing ends of a principal axis of macroscale structural-functional cortical organization separating unimodal sensory and motor regions from higher-order, heteromodal association cortices. We argue that explicit learning is supported by task-general functional networks specialized for the encoding of high-level task structure, and for the assimilation of action-outcome association spanning multiple trials in episodic memory, and that the computations underlying these processes are facilitated by structural and neurophysiological differences between unimodal and heteromodal cortices.

Disclosures: C.N. Areshenkoff: None. **A.J. De Brouwer:** None. **D. Gale:** None. **J.Y. Nashed:** None. **J. Flanagan:** None. **J.P. Gallivan:** None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

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Program #/Poster #: PSTR279.17/FF6

Topic: E.05. Brain-Machine Interface

Support: Allen Institute
HHMI
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Shanahan Family Foundation Fellowship (to M.S.B and L.M)
University of Washington
Swartz Foundation Postdoctoral Fellowship (to F.L.)
NIH-NIMH Award K99/R00-MH121533 (to M.D.G.)

Title: Local circuit plasticity in motor cortex during learning

Authors: *M. S. BULL[1], M. ROZSA[2], F. LAGZI[3], L. MI[1], P. HUMPHREYS[4], M. ECKSTEIN[4], Z. KURTH-NELSON[4], K. L. STACHENFELD[4], T. LILLICRAP[4], C. CLOPATH[5], M. M. BOTVINICK[4], K. SVOBODA[2], K. DAIE[2], M. D. GOLUB[1];
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Abstract: Learning a new task or skill involves synaptic plasticity that drives new patterns of activity in cortical circuits. Network models of learning have shown that learning can be driven by a variety of plasticity mechanisms including modification of long-range inputs, local synaptic plasticity and/or modifications of cell intrinsic properties. However, the degree to which these mechanisms contribute to learning is unknown. To explore the circuit mechanisms involved in learning we developed a robust optical brain computer interface (BCI) task, which we combined

with two-photon photostimulation to map learning-related changes in local connectivity. Mice learned to modulate the activity of a single 'conditioned neuron' (CN) in layer 2/3 of motor cortex to obtain reward. Mice improved the rate of rewarded trials from 55% to 75 % within the first 25 trials (5 minutes). Small groups (~ 10/500 per experiment) of 'enhanced neurons' increased their activity at a similar level to the CN. Photostimulation before and after learning revealed changes in cortical connectivity that were correlated with learning. The enhanced neurons increased their within-ensemble connectivity after learning. To better understand mechanisms underlying these learning-related changes in activity and connectivity, we developed recurrent neural network (RNN). With these models, we tested three potential mechanisms of learning: 1. 3-factor Hebbian plasticity of local synapses, 2. Changes in activity in long-range inputs, and 3. Changes in excitability of individual neurons. We found that all mechanisms could produce learning-related changes in CN activity. However, only local synaptic plasticity and changes in excitability were able to recapitulate the observed changes in connectivity within the learning ensemble. In contrast, activity changes in long-range inputs to the RNN produced non-specific changes in local connectivity. These results suggest that local plasticity in cortical circuits may be involved in fast learning.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.18/FF7

Topic: E.04. Voluntary Movements

Support: CONACYT Ciencia Básica A1-S-8686 (GR-P)
UNAM-DGAPA PAPIME PE205821 (RO-M)
UNAM-DGAPA PAPIIT IN201121 (GR-P)
CONACyT fellowship 858704 (MM)
CONACyT fellowship 934183 (MA-C)

Title: Dynamics of corticospinal ensembles activity throughout motor learning

Authors: *M. MACÍAS[1], M. ALTAMIRA-CAMACHO[1], R. OLIVARES-MORENO[1], M. LOPEZ-HIDALGO[2], G. ROJAS-PILONI[1];
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Abstract: The ability to learn motor skills involves an improvement in accuracy, speed and consistency of movements. Motor control is related to movement execution and involves

corticospinal neurons (CSp), which are located in layer 5B of the primary motor (M1) and somatosensory (S1) cortices. M1 CSp neurons are functionally diverse, and is poorly explored if different classes of CSp change their activity throughout motor learning. It has shown that the population activity of M1 and S1 CSp neurons changes with learning and is different between both cortices. However, it is unknown whether these changes are due to subsets of CSp neurons within the population and how the activity of these subsets is related to different aspects of a learned movement. Given the importance and interaction between M1 and S1 related to movement, we investigated this issues in CSp neurons located in the sensorimotor cortex (SMC). We induced the expression of a jGCaMP7s calcium indicator to analyze motor-related Ca^{2+} transient dynamics of CSp neurons from SMC while C57Bl/6 wild-type adult mice learned and performed a cued lever-press task. In addition, we obtained the kinematic aspects of behavior to relate them to neuronal activity. CSp neurons exhibited correlations in their activity between them, forming ensembles throughout the training sessions. Furthermore, the activity of the different ensembles was more related to movement phases of the behavioral task, i.e., reaching movement, pressing and release of the lever with learning. These results suggest the association between corticospinal ensembles activity and movement changes as movement is learned and refined.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.19/FF8

Topic: E.04. Voluntary Movements

Support: Max Planck Florida Institute for Neuroscience
Max Planck Free Floater Program
NIH New Innovator Award (NINDS and OD; 1DP2NS132108)
Searle Scholars Program
Klingenstein-Simons Fellowship
McKnight Scholar Award

Title: Experience-dependent motor timing adaptation in ALM

Authors: *Z. YANG, S. MAJUMDER, M. INAGAKI, H. INAGAKI;
Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: Animals continually adapt behaviors to survive in the ever-changing environment. To do so, animals explore the environment through actions and update future movements based on the outcomes. Yet, how the brain encodes past experiences to influence future movements remains unclear. To fill this gap, we developed a motor timing task where adult mice (both

sexes) acquire a reward by licking after a delay following a cue signaling the trial onset. When we randomly switched the delay duration in a block of trials without signaling the delay duration (switching delay condition, 22 mice), mice rapidly adapted lick times (~ 10 trials). A linear regression model indicates that mice use trial history (lick times and reward outcomes in the last few trials) to guide future lick times properly. In contrast, when we fixed the delay duration in all trials (fixed delay condition, 20 mice), they stopped using trial history, likely because they learned the set timing. By leveraging optogenetics and *in vivo* large-scale electrophysiology, we systematically compared the neural dynamics underlying these two conditions (the same task structure but with or without trial history-dependent adaptation) to identify the neural mechanisms of adaptive motor timing. First, optogenetic loss-of-function screening of the dorsal cortical areas shows that the anterior lateral motor cortex (ALM) is required for motor timing and lick execution in both conditions, consistent with ALM's known role for planning and execution of lick. Second, we performed extracellular electrophysiology in ALM, and identified two activity modes that explain a large proportion of population activity before lick: 1) persistent mode, which shows persistent activity between trials and transient response upon cue presentation, and 2) ramping mode, which ramps up gradually before lick. In both task conditions, the slope of ramping mode predicts lick time, in line with literature showing that ramping preparatory activity determines action timing. Intriguingly, the amplitude of the activity along the persistent mode before the trial and during the cue encodes trial history and predicts future lick time only in the switching delay condition. In addition, manipulating activity along the persistent mode changed the ramping mode activity and lick times only in the switching delay condition, indicating the causality between these modes and behavior. Together, we identified the dynamics linking the past experiences and future actions: persistent spiking activity encodes past experiences across trials, and sets the initial state of the ALM dynamics to alter the ramping preparatory activity that determines the upcoming lick time.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

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Topic: E.04. Voluntary Movements

Support: Max Planck Florida Institute for Neuroscience
Max Planck Free Floater Program
NIH New Innovator Award (NINDS and OD; 1DP2NS132108)
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McKinght Scholar Award

Title: Cell-type-specific plasticity shapes neocortical spiking dynamics during motor learning

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Abstract: The neocortical spiking dynamics control aspects of behavior, yet how these dynamics emerge during motor learning remains elusive. The primary hypothesis is activity-dependent synaptic plasticity, as it can reconfigure network architectures that govern neural dynamics. Here, we examined how the mouse premotor cortex acquires its well-characterized neural dynamics that control the timing of movement. We developed a timing task where mice gradually learn to delay lick timing following a cue to obtain a reward, and acutely manipulated proteins involved in synaptic plasticity during learning. Specifically, we transiently inactivated Calcium/Calmodulin-dependent protein kinase II (CaMKII), a kinase essential for major forms of synaptic plasticity, using a genetically encoded light-inducible inhibitor of CaMKII, paAIP2 (photoactivatable autocamtide inhibitory peptide 2). PaAIP2 manipulation in the anterior lateral motor cortex (ALM; premotor cortex responsible for orofacial movement), but not the primary motor cortex (M1), blocked learning of new lick timing without affecting the execution of learned movements or ongoing spiking activity (n >= 4 mice per condition). The major excitatory cell types in the neocortex include pyramidal tract (PT) and intratelencephalic (IT) neurons, projecting outside and within the telencephalon, respectively, both of which highly express CaMKII. Notably, paAIP2 manipulation in PT neurons in ALM, but not IT neurons, impeded learning (n >= 6 mice per condition). We employed two additional acute cell-type-specific genetic manipulations that affect synaptic plasticity: CRISPR/Cas9 knockout of CaMKIIα (CaMKII isoform required for synaptic plasticity) and optogenetic inactivation of Cofilin (also required for major forms of synaptic plasticity). Both reproduced the necessity of ALM PT neurons but not IT neurons for learning new lick timing. Furthermore, by combining large-scale electrophysiology with cell-type-specific paAIP2 manipulation, we discovered that neural dynamics in the ALM progressively alter during learning, in a manner distinct from how activity changes when lick time fluctuates in expert animals, and such reconfiguration requires CaMKII activity in PT neurons (recorded 2704 neurons in ALM from 26 mice). Although nearly all cell types could induce synaptic plasticity, our findings support that they are not redundant. Instead, plasticity-related protein activity in a specific cell type, PT neurons, is required for sculpting neocortical dynamics to achieve new behavioral goals.

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Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.21/FF10

Topic: E.04. Voluntary Movements

Support: NIH Grant R01 NS129551 (MO)
NIH Grant R21 NS101499 (MO)
CNSI & NINS BS291006 (MO)

Title: Effect of DNA methylation inhibition in monkey primary motor cortex on performance of sequential movements after extensive practice

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Abstract: The acquisition of an expert level of performance of sequential movements requires extensive practice. Recent studies in monkeys indicate that extensive practice on sequential movements alters patterns of neural and functional activation in the primary motor cortex (M1) (Matsuzaka et al., 2007; Picard et al., 2013), and that manipulation of M1 disrupts the performance of acquired sequential movements (Ohbayashi, 2020). These findings and others led us to hypothesize that M1 becomes a site of long-term storage of the acquired sequential movements and remains critical for maintenance. To test this hypothesis, we injected an inhibitor for DNA methylation into M1 after extended practice of sequential movements. Change in DNA methylation has been shown to underlie the long-lasting maintenance of memory in the face of continued protein turnover (Miller et al., 2010; Jarome et al., 2014). We trained two monkeys (*Cebus apella*) on two tasks (Matsuzaka et al., 2007, Ohbayashi 2020). In the Random task, new visual targets were presented in a pseudorandom order, 100 ms after contact of the prior target. Therefore, the monkeys performed the reaching movements guided by the visual cues. In the Repeating task, visual targets were presented according to a repeating 3 element sequence (e.g., 234234 ...). New targets were presented 400 ms after contact of the prior target. The longer delay promoted the monkey to predict the next target in the sequence. With practice, monkeys reached the correct targets before the presentation of the visual cues. Therefore, the monkeys performed memory-guided sequential movements in this task. We injected an inhibitor for DNA methylation (2-3µl of 200 ng/µl 5-azadeoxycytidine) into M1 after more than 170 days of training and tested its effect on performance of the tasks. We analyzed the monkeys' behavior before and after the injection separately for each movement in each task. The injection had a significant effect on the performance of the movements during the Repeating task, but not during the Random task. In the Repeating task, the error rate for the most affected movements increased by 71 % after the injection. In 64% of trials, the monkey reached in the direction opposite to the correct target. In addition, response time in the Repeating task increased significantly. Notably, the monkey needed to be retrained for more than 20 days to recover the performance of the Repeating task to the pre-injection level. These effects were consistent over four injections in two monkeys (Monkey 1, n=3; Monkey 2, n=1). The results support the concept that M1 remains critical for maintenance of skilled sequential movements even after extensive practice.

Disclosures: M. Ohbayashi: None.

Poster

PSTR279. Motor Learning of Skilled Behaviors

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.22/FF11

Topic: E.04. Voluntary Movements

Support: ISF 1684/20

Title: Refinement of motor control: from coarse to fine movements in freely behaving zebrafish

Authors: Y. RUBINSTEIN[1], M. MOSHKOVITZ[2], S. TIOMKIN[4], ***L. AVITAN**[3];
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Abstract: The outcome of zebrafish movement in shallow, approximately 2d-environments, is theoretically defined by three variables. A common assumption is that two of these variables - swimming distance and the change in heading direction - are sufficient to fully describe the outcome of fish movement. This assumption neglects the third variable - azimuth angle, the direction along which the fish moves. We examined the relationship between the three variables and found that in the common case of coarse movements, these variables are correlated, and fish movements can be described by two variables, compatible with current literature. However, in cases where fine and more accurate movements are required, this dependency breaks, and a third variable is required to get an unambiguous description of the fish movement. We demonstrated this increase in movement dimensionality in larval zebrafish hunting behavior. Fine motor control is implemented throughout the hunting sequence, hence verifying that three parameters are required for a complete and accurate movement description. These findings provide a biological manifestation of the 'control refinement principle', where control is firstly applied in a coarse, low-resolution manner, followed by refinement with more precise control in a higher-resolution space. Moreover, we show that even in the common case, when two parameters are sufficient, using the full, three-parameter description sheds new light on the way zebrafish implement their hunting strategy. Together, it provides a complete and more accurate framework to analyze fish behavior.

Disclosures: Y. Rubinstein: None. **M. Moshkovitz:** None. **S. Tiomkin:** None. **L. Avitan:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.01/FF12

Topic: E.05. Brain-Machine Interface

Support: AHA Postdoctoral fellowship 897265
CNSM Postdoctoral fellowship D000000101
NIH 4R00NS097620
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AHA Career Development 847486
NIH R01NS128469
AHA 23PRE1018175

Title: Cortico-cerebellar mechanisms of neuroprosthetic control

Authors: *A. ABBASI[1], R. RANGWANI[2,1], D. BOWEN[1], A. FEALY[1], N. DANIELSEN[1], T. GULATI[1,2];
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Abstract: Introduction: Brain-machine interfaces (BMIs) or neuroprosthetics allow neural control over assistive devices. They also provide an important framework for studying neural plasticity in the sensorimotor networks . To understand the neural mechanisms of skill learning in cortico-cerebellar networks, we performed electrophysiologic recordings in the motor cortex (M1) and the cerebellum (Cb) of rodents while they engaged in M1-driven BMI control. We found that both regions' neurons developed task-related (*TR*) modulation, and this was coordinated with an emergent 3-6Hz oscillatory activity in the M1 and Cb local field potentials (LFPs). We also found that Cb optogenetic inactivation (at the level of Cb cortex or its deep nuclei) caused task impairments. **Methods:** We recorded single units and LFPs in adult Long-Evans rats (n=7) while they performed a neuroprosthetic task by implanting microwire arrays in M1 and tetrodes/polytrodes in Cb. During the task, activity of a subset of M1 neurons was transformed into the angular velocity of a feeding tube using a linear decoder. Rats modulated the activity of these 'direct' neurons (M1 TR_d) to obtain water reward. We analyzed how the activity in these neurons, as well as all other recorded 'indirect' neurons in M1 and Cb changed while learning the BMI task. We also analyzed band-limited oscillatory activity in both regions. Furthermore, we performed optogenetic silencing of Cb cortex and the deep nuclei in two groups of rats (n=3/ group), while they performed the BMI task and analyzed how silencing affected M1 activity and BMI control. **Results:** We found that learning BMI control was associated with the modulation of M1 TR_d, as well as robust task-related 'indirect' (TR_i) modulation in M1 and Cb. We also observed a 3-6 Hz synchronous oscillatory activity in M1-Cb LFPs which coordinated task-related neural spiking. We found that the canonical correlation between task-related M1 and Cb spiking activity increased with learning. Furthermore, we found that Cb TR_i activity well-predicted M1 TR_d and TR_i activity but not M1 task-unrelated activity (M1 *TU;* as analyzed through spike generalized linear models). We also found that optogenetic inhibition of Cb cortex and its deep nuclei weakened M1 *TR* activity and led to performance impairments in the BMI task. **Conclusion:** Our work has identified neural mechanisms in M1-Cb which are associated with learning of a M1-driven neuroprosthetic skill. This underscores the importance of optimal engagement of neural learning mechanisms in the larger motor network for learning proficient neuroprosthetic control.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.02/FF13

Topic: E.05. Brain-Machine Interface

Support: AHA Predoctoral fellowship 23PRE1018175
NIH R00NS097620
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Title: Robust neuroprosthetic control using cerebellar activity in the stroke brain

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Abstract: Over the years, impressive studies in rodent, non-primates and clinical applications in humans have demonstrated that activity of sensorimotor neocortical areas can be decoded as a control signal to replace lost motor function using brain-machine interfaces (BMI). Surprisingly, subcortical regions such as the cerebellum (Cb) have not received much attention for implementing direct neural control, despite studies revealing that Cb cortical neurons exhibit tuning to limb position, velocity, duration, and muscle activity during voluntary arm movements. It is important to study if Cb direct neural control is feasible, as cortical areas such as primary motor cortex (M1) are not viable for direct neural control after an injury like stroke. We validated the use of direct Cb cortical neural activity in a neuroprosthetic task in healthy/stroke rodent models as well as studied cortico-cerebellar interactions. We recorded single-units and local-field potentials (LFPs) from drivable polytrodes in the Cb cortex as well as microelectrodes in M1 while adult healthy long-Evans rats (n=11) performed a neuroprosthetic task using the M1 or Cb activity. Additionally, we conducted Cb BMI experiments in a cohort of M1-stroke injured animals (n=4; photothrombotic stroke), to test viability of Cb neural activity for BMI application with an injured M1. During the task, rats exerted control over the angular velocity of a water tube by modulating activity of a subset of experimenter defined Cb neurons, classified as ‘direct’ neurons and using a simple linear decoder (Gulati et al, 2017; Kim et al, 2019). Our results show that efficient Cb-driven BMI control is possible, and it is as robust as M1-driven control. We observed that direct Cb neurons develop robust task-related modulation as seen in M1-driven BMIs. Remarkably, robust learning was also seen in rats recovering from stroke that had their forelimb motor function compromised (assessed on a reach-to-grasp task). Furthermore, we observed extensive indirect task-related modulation in both Cb and M1. We found that synchronous 3-6 Hz oscillations emerged in M1-Cb LFPs as Cb-driven neuroprosthetic control was learned. Using regression, we found that Cb/M1 indirect activity predicted the Cb direct activity, but the timescale was different for local vs cross-region interactions. Cb BMI behavioral performance remained the same in M1-stroke injured vs healthy brain while cortico-cerebellar

interactions were affected post-stroke. Our work demonstrates feasibility of direct BMI control using Cb activity when M1 is stroke-injured, and elucidates the cortico-cerebellar neural mechanisms facilitating such control.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.03/FF14

Topic: E.05. Brain-Machine Interface

Support: NINDS Grant F31NS129099
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Title: Instruction modality modulates neurons in cortical motor areas.

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Abstract: Primary motor cortex (M1) and premotor cortex (PM) both participate in control of voluntary movements. M1 is commonly thought to execute movements while PM plans them, but these traditional roles do not fully explain the activity of M1 and PM neurons. For example, neurons in both areas were recently shown to be modulated by reward information – a factor seemingly independent of movement planning or kinematics. Might M1 and PM neurons be influenced by other non-kinematic factors? Here, we investigated whether the activity of M1 and PM neurons varied based on the modality with which the instruction was delivered, even when the instruction was for the same movement having the same reward. Two male rhesus monkeys were initially trained to reach to, grasp, and manipulate 4 different objects instructed by visual cues (LEDs), and then were implanted with microelectrode arrays in M1, PM, and the primary somatosensory cortex (S1). Subsequently, the monkeys were trained to perform the same task with ICMS instructions instead of the visual cues. ICMS instructions were delivered through a set of 3-7 electrodes on a different array in S1 for each object (1-64μA per electrode, 75 – 150Hz). Ultimately, visually- and ICMS-instructed trials were randomly interleaved while recording neural data from M1 and PM. From such sessions, we analyzed 39 M1 units and 42 PM units (both single- and multi-units) in one monkey; 36 M1 units and 33 PM units in the other. We rendered spike trains from visually- and ICMS-instructed trials comparable by convolving spike trains from the visually-instructed trials with trains of blanking windows that emulated collisions between spikes and ICMS pulse artifacts. We then compared the firing rates of each neuron between visually- and ICMS-instructed trials for each object separately (neuron-array pairs). We initially examined only neuron-array pairs in which ICMS pulses produced no direct modulation (DM-) of the neuron's activity in peri-stimulus time histograms triggered on

the ICMS pulses. For many DM- neuron-array pairs, neural activity was significantly different between visually- and ICMS-instructed trials, which we term “instruction-modality modulation” (IM). In M1, 14/34 (41%) of DM- pairs from monkey L and 14/36 (39%) from X displayed IM. For DM- PM pairs, 39/93 (42%) from L and 19/38 (50%) from X displayed IM. We also found IM in neural activity from neuron-array pairs that were directly modulated by S1-ICMS (DM+). Including both DM- and DM+ pairs, 102/144 (71%) of M1 pairs in L and 65/103 (63%) in X showed IM; 76/151 (50%) of PM pairs in L and 57/87 (66%) in X showed IM. The majority of neuron-array pairs in both M1 and PM were modulated by instruction modality.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.04/FF15

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01 NS107271
NIH Fellowship 1F31 NS129099

Title: The effects of low-amplitude intracortical microstimulation in one cortical area don’t stay in that cortical area

Authors: *B. M. RUSZALA[1], M. H. SCHIEBER[2];
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Abstract: Although the effects of electrical intracortical microstimulation (ICMS) are commonly assumed to activate only neurons near the tip of the stimulating electrode, ICMS effects are largely transsynaptic and can reach neurons far from the stimulation site. For example, ICMS delivered in the primary motor cortex (M1) can activate distant spinal motoneurons via corticospinal projections, evoking contractions in distal forelimb muscles. Similarly, the effects of ICMS delivered in one cortical area may not be confined to that area, potentially modulating the activity of neurons in distant cortical areas via cortico-cortical connections. Here, we examined the extent to which ICMS delivered in the primary somatosensory cortex (S1), ventral premotor cortex (PMv), or anterior intraparietal area (AIP) of rhesus macaques modulated neural activity in several distant cortical regions of the reach-to-grasp network: PMv, dorsal premotor cortex (PMd), M1, S1, AIP, and dorsal posterior parietal cortex (dPPC). Two male rhesus monkeys (Q, F) were initially trained to choose among 4 targets in a center-out target task instructed by visual cues, and then were implanted with microelectrode arrays in PMv, PMd, M1, S1, AIP, and dPPC. Subsequently, the visual instructions for the 4 targets were replaced by ICMS instructions delivered in one cortical area: S1, PMv, or AIP. Instructions were delivered as trains of simultaneous pulses through different sets of 4 electrodes for each target (20 - 35µA per electrode, 12.5-30ms jittered inter-pulse intervals). Neural data were recorded from the other 5

non-stimulated cortical areas as the monkey performed the task with S1-ICMS, PMv-ICMS, or AIP-ICMS instructions. In each monkey, we constructed peristimulus time histograms (PSTHs) using the spike times of each single- or multi-unit, triggered on the individual pulses of each ICMS instruction recorded in the first session ICMS was delivered in a given cortical region. We considered a unit to be directly modulated by ICMS if the corresponding PSTH was either significantly non-uniform (KS goodness of fit test, p < 0.01), or contained a significant peak or trough (±2 standard deviations of the baseline for 3+ bins). We found that S1-ICMS, PMv-ICMS, and AIP-ICMS each directly modulated neurons in all other implanted areas. ICMS with an amplitude of 35µA or less delivered in one cortical area directly modulated neurons across the cortical reach-to-grasp network.

Disclosures: B.M. Ruszala: None. **M.H. Schieber:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.05/FF16

Topic: E.05. Brain-Machine Interface

Support: Horizon-EIC-2021-Pathfinderchallenges-01-02 NEMO-BMI 101070891
Institut Carnot Leti

Title: Auto-adaptive and embedded decoding algorithms for WIMAGINE ECoG-based BCI for motor compensation

Authors: H. LAFAYEDEMICHEAUX[1], J. SAAD[2], A. EVANS[3], I. MIRO-PANADES[2], L. STRUBER[4], H. LORACH[5], S. CHABARDES[7], J. BLOCH[8], A. GALVEZ[6], G. COURTINE[9], S. KARAKAS[10], F. MARTEL[11], V. JUILLARD[1], P. KOPRINKOVA[12], N. KASABOV[12], J. DEDELLEY[13], P. HECK[13], J. VLACHOS[13], V. DELATTRE[13], J. MURPHY[13], G. CHARVET[14], ***F. SAUTER-STARACE**[15], T. AKSENOVA[16];
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Abstract: After several remarkable First in human clinical Trials, the Brain Computer Interface (BCI) Community is now striving for daily life use of motor handicap compensation or communication solutions. Our project benefits from WIMAGINE®, the 64 channels ECoG recorder and the software suite designed and manufactured by CEA Leti Clinatec to record and

decode in real-time the brain signals. Based on the results of two groundbreaking BCI clinical trials (NCT02550522, NCT04632290), we demonstrated the reliability and the promises of our BCI systems for tetraplegic or paraplegic patients using supervised algorithm and as an effector the exoskeleton [1] or the implantable spinal cord stimulator [2]. To work toward home use, we propose the auto-adaptive framework for unsupervised use of the decoder [3]. We adapted this strategy to gait trainings sessions, the self-adaptive unsupervised model recalibration was 24% better than random auto-adaptive training and 26% lower than to the supervised recalibration. We are working also on a neuromorphic decoding and self-adaptation real time algorithms that will be implemented in neuromorphic hardware in near future.In addition, we have started the optimization the decoding algorithms first by a full translation and acceleration in C++ to be able to run the decoding software on a portable platform such as a Raspberry pi hardware achieving decoding in less than 100 ms, which was our target to perform real-time decoding. In addition for sake of portability, a second objective is the miniaturization of the decoding hardware by designing an integrated circuit dedicated to ECoG based BCI decoding.[1] Benabid, Alim Louis, et al. "An exoskeleton controlled by an epidural wireless brain-machine interface in a tetraplegic patient: a proof-of-concept demonstration." *The Lancet Neurology* 18.12 (2019): 1112-1122.[2] Lorach, Henri, et al. "Walking naturally after spinal cord injury using a brain-spine interface." *Nature* (2023): 1-8.[3]: Rouanne, et al, T. (2022). Unsupervised adaptation of an ECoG based brain-computer interface using neural correlates of task performance. Scientific Reports, 12(1), 21316.**Acknowledgements**: Horizon-EIC-2021-Pathfinderchallenges-01-02 NEMO-BMI 101070891) and Institut Carnot Leti.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.06/FF17

Topic: E.05. Brain-Machine Interface

Support: NIH Grant RF1AG060754

Title: Cortical release of acetylcholine to deep brain stimulation of the sub pallidal forebrain in mice

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of Neurosci. & Regenerative Med., Augusta, GA; [4]Neurosci. and Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA

Abstract: Over 160k patients have received deep brain stimulation (DBS) implants and their use is growing. We have documented that chronic, one hour daily, intermittent stimulation of the sub-pallidal basal forebrain (BG) increases cortical levels of acetylcholine (ACh) and makes animals smarter. However, the dynamics of ACh release in response to DBS has not been sufficiently documented. Using fluorescent acetylcholine (GACh3.0) reporters in mice and 2-photon in vivo imaging we aimed to quantify ACh changes in response to DBS with the resolution of seconds. We stimulated the BG with 60Hz for 60s and recorded fluorescence change to a 10s test pulse every 5mins. Our data suggests that 1) depletion of the ACh response occurs within 60s; the physiologic half life of ACh release is likely 10-12s and 2) the recovery time from depletion is within 20mins; recovery time per second of stimulation is likely 10-12s. This study is ongoing and future studies will include manipulation of acetylcholinesterase and the choline transporter to examine mechanisms.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

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Program #/Poster #: PSTR280.07/FF18

Topic: E.05. Brain-Machine Interface

Support: NIH GRANT K00NS118719

Title: Long-term sensorimotor cortex sensing using permanently implanted subgaleal leads in a patient receiving deep brain stimulation for Parkinson’s disease

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Abstract: Pathological oscillatory activity in cortico-basal ganglia (BG) circuits is linked to motor symptoms in Parkinson's disease (PD). Sensing-enabled deep brain stimulation (DBS) devices connected to subdural electrocorticography (ECoG) leads over sensorimotor cortex show that changes in synchronized oscillatory activity across the cortex-BG motor network correlate with motor signs and therapeutic response. Advances in adaptive DBS, which adjusts stimulation based on neural signals and changing brain states, requires identification of neurophysiological biomarkers that correlate with various motor symptoms. Cortical biomarkers have shown promise as feedback signals for adaptive DBS, but limited studies exist due to the invasiveness of subdural ECoG paddles. Using less invasive under-the-scalp (e.g., subgaleal; SG) permanent

leads to record cortical activity would reduce risks associated with placing permanent electrodes directly on the brain's surface and enable rapid scalability, inclusivity, and equitable access to adaptive DBS for PD using cortical signals. An individual with PD was implanted with bilateral sensing-enabled DBS devices, each connected to a directional lead targeting the subthalamic nucleus (STN) and a cortical lead placed in the SG space over sensorimotor cortex. For cortical sensing, an octopolar 10.5 mm segmented DBS lead was implanted over one side and an octopolar 57 mm paddle type lead, normally used for spinal cord stimulation, was implanted over the other side. At various time points post-implantation, we recorded local field potentials from both the STN and SG leads while the study participant was at rest either OFF stimulation or during STN stimulation amplitude titrations. We found that both SG leads were able to detect low frequency beta sensorimotor activity at rest and OFF STN stimulation. During stimulation amplitude titrations, the segmented SG lead, but not the paddle type lead, detected finely tuned cortical gamma entrainment at half the stimulation frequency (62.5 Hz) while on 4.0 mA STN stimulation. Cortical entrained gamma corresponded with a 62.5 Hz finely tuned gamma peak observed in the STN with 4.0 mA stimulation. These findings suggest that SG cortical recording from a permanent implant can detect sensorimotor activity in physiologically relevant frequency bands. Cortical finely tuned gamma (FTG) activity is a promising feedback signal for adaptive DBS. SG lead detection of cortical FTG suggests that SG sensing may be used in studies of adaptive DBS. Ongoing studies are investigating sensorimotor activity during various brain states, including on/off DBS, on/off medication, and during movement vs rest.

Disclosures: S. Sandoval-Pistorius: None. **R. Fernandez-Gajardo:** None. **S. Cernera:** None. **P.A. Starr:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.08/FF19

Topic:

Support: NIH NINDS UH3 NS100544

Title: Deep brain stimulation-induced entrainment of cortical finely tuned gamma oscillations: effects of voluntary movement in Parkinson's disease

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Abstract: *Objective:* To study the role of voluntary movement in bilateral entrainment of finely tuned gamma oscillations (FTG) in the sensorimotor cortex via unilateral subthalamic deep brain stimulation (DBS).
Background: Prior studies show that FTG activity is associated with a prokinetic state and

increases with movement. We have previously described cortical gamma entrainment, or induction of FTG at a subharmonic of the stimulation frequency. DBS-induced FTG entrainment may be related to improved movement in Parkinson's disease (PD).
Methods: We recorded basal ganglia and sensorimotor cortex local field potentials in-clinic from six hemispheres of three PD patients receiving bilateral subthalamic nucleus (STN) DBS. Patients were implanted with an investigational bi-directional DBS device with subdural electrocorticography leads. We performed unilateral frequency-amplitude titrations, while off contralateral DBS therapy. The time subjects spent at each frequency-amplitude combination was divided between remaining at rest and completing a standardized finger-tapping task. We determined the amplitude of gamma entrainment present in both hemispheres using the FOOOF algorithm, and computed average FTG power over several time intervals during finger tapping to relate variability of gamma entrainment amplitude across time to the different stages of a voluntary movement.
Results: In all patients, we observed cortical FTG entrainment at half the stimulation frequency at a select set of frequency-amplitude combinations during movement and rest in both pre- and postcentral gyri. The amplitude of entrainment was larger during movement than during rest and in precentral gyrus than in postcentral, across parameter combinations and subjects. Entrainment was not linearly related to stimulation amplitude, decreasing with increasing stimulation amplitudes at select frequencies. In the precentral gyrus, and at 90 - 130 Hz stimulation only, we observed increased FTG activity during the first 3-6 seconds following movement onset that waned over time. Lastly, we report contralateral hemisphere FTG in two of three patients, at a narrower range of frequencies than ipsilateral entrainment.
Conclusions: We demonstrate specificity of ipsi- and contralateral FTG region and movement-related characteristics of DBS-induced entrainment unique to the precentral gyrus that may underlie the mechanism of motor regulation in PD. Contralateral cortical entrainment could be the physiological basis for the ipsilateral motor effects of therapeutic DBS described in prior reports. Next, we will relate these observations to their clinical manifestations.

Disclosures: M. Shcherbakova: None. **S. Cernera:** None. **A. Hahn:** None. **S. Little:** None. **P.A. Starr:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.09/FF20

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01 NS121079

Title: Independent use of an at-home intracortical BCI system

Authors: *W. HOCKEIMER[1,2], J. M. WEISS[1,2], B. M. DEKLEVA[1,2,4], D. WEIR[1,2], N. G. KUNIGK[1,3], S. M. CHASE[4,5,6], M. L. BONINGER[1,2,3], J. L. COLLINGER[1,2,3,4,5];

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Abstract: A long-term goal of intracortical brain-computer interface (iBCI) research is to allow people with motor impairments to use iBCIs independently at home. A significant impediment to that goal is that iBCI use typically requires expert assistance to achieve good control and relies on cumbersome hardware systems. Here we present initial use of an upgraded version of our previously described at-home system, which had limited computational capabilities and battery life (Weiss et al., 2019). The participant is a 36-year-old man with tetraplegia due to cervical spinal cord injury with intracortical electrodes implanted in motor and sensory cortices. Updated neural recording hardware (Blackrock Neurotech, Salt Lake City, UT) was approved for independent use under an FDA Investigational Device Exemption. 256 channels of data are acquired and processed by a compact Neural Signal Processor that connects to AC power and these data are streamed via gigabit ethernet to a commercially-available tablet with 32 GB RAM and a 1 TB SSD. The participant and his caregivers were trained to operate the system prior to use. A custom mount is used to attach the recording hardware to the participant's wheelchair. The caregiver connects the implant pedestals to the iBCI system while the participant, who retains residual motor function of his proximal arm, initiates the software on the tablet touchscreen. During testing the participant first calibrates a decoder and completes a gamified click-and-drag center-out task (Dekleva et al., 2021). The participant can use a GUI to change cursor gains and biases. After an initial prototyping period, three sessions were collected to quantify performance. Performance at home was similar to 20 comparable lab sessions, with an average of 95% ± 5% trials correct compared to 88% ± 17% in lab. The mean path inefficiency (real path / ideal path) was 1.86 ± 0.12 compared to 1.88 ± 0.74 in lab; the mean target acquisition rate was 3.6 ± 0.84 targets / min compared to 4.4 ± 1.65 targets / min in lab; and the mean click time was 2.55 ± 1.5 s versus 1.66 ± 1.03 s in lab. The participant rated satisfaction with the iBCI system on scale from 0 to 10 (maximally satisfied) with an average of 7.6 ± 1.5 / 10. The NASA TLX (Hart and Staveland, 1988) was used to assess subjective task load on a 100 point scale (100 = highest load) with 5 point increments. The average weighted score of 5.74 ± 3.36 was lower than the average lab score of 19.13 ± 13.38, suggesting that iBCI use is no more difficult at home versus lab. These data demonstrate initial use of an improved at-home iBCI system. Further work will primarily focus on collecting long-term usage data and increasing online functionality to improve control.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.10/FF21

Topic: E.05. Brain-Machine Interface

Title: Spatial and Spectral Changes in Cortical Surface Potentials during Pinching versus Thumb and Index Finger Flexion

Authors: *P. KEREZOUDIS[1], M. JENSEN[2], H. HUANG[2], J. ROTTER[1], J. G. OJEMANN[4], D. HERMES[3], K. J. MILLER[2];
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Abstract: Rationale: Electrocorticographic (ECoG) signals can resolve the activation of the sensorimotor cortex and the somatotopic representation of contralateral hand movements with high accuracy. The relationship between individual or synergistic finger movement and the corresponding ECoG neural signals has not been fully explored.**Objective:** To compare the spatial cortical representation of pinching versus thumb and index finger flexion. **Methods:** We analyzed the electrocorticographic signals of 3 patients (2 females, aged 18-21-19 years) implanted with subdural electrode arrays for identification of seizure foci. Patients were asked to perform screen cue-based flexion movement of the thumb or index finger, or a pinch movement of both. Hand movements were captured by a data glove simultaneously with ECoG recordings. Broadband power changes with each movement were estimated using a well-established principal component analysis of the power spectrum. Topological maps for each type of movement were created using CT-MRI co-registered brain renderings, and the overlap in spatial extent was quantified using a resampling metric.**Results:** Significant increase in broadband power was observed in all three patients when pinch (max signed r^2 0.67-0.84-0.82), thumb flexion (0.67-0.89-0.72) or index flexion (0.65-0.89-0.72) was performed compared to rest. Spatial overlap was significant between thumb and index flexion in all three subjects (60-70%), while spatial overlap between pinch and index flexion (67-90%, all $p<.001$) was considerably higher compared to pinch and thumb flexion (23-77%; significant in 2/3 patients). Finally, the geometric mean of thumb/index flexion resulted in similar results to the pinch-index comparison, with significant overlap in 2/3 subjects (82-89%) and 31% in one patient.**Conclusion:** For pinch, the ECoG signal seems to comprise a combination of the signals from the individual thumb and index movements, with considerably larger overlap with the latter. This analysis may provide insights into motor cortex tuning toward specific types of motor behaviors.

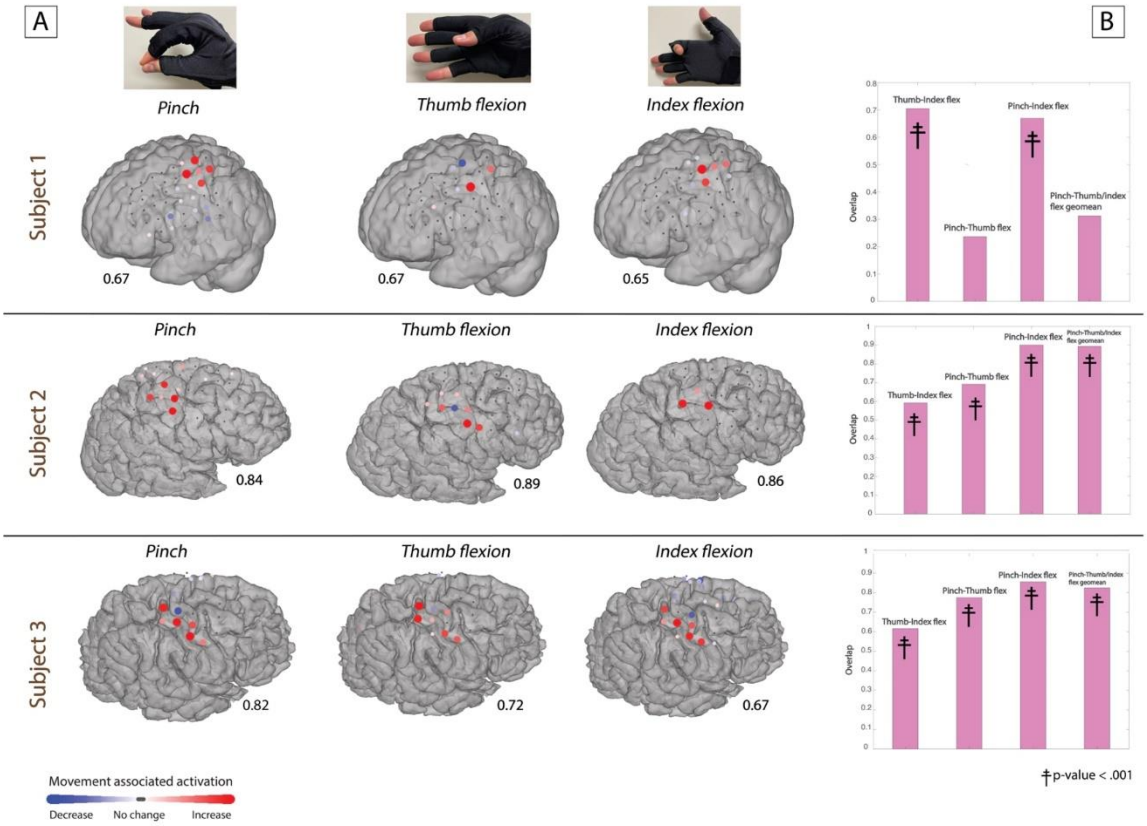

Figure legend. ECoG broadband power resolves somatotopic representation of finger movement. (A) Changes in broadband power at different cortical sites for pinching (left panel), thumb flexion (middle panel) and index finger flexion (right panel). Colors denote a signed R-squared measurement of increases and decreases in power with movement relative to rest (with maximum denoted in the lower left or right corner). (B) Quantification of spatial overlap between changes associated with the different types of finger-movements (1 is maximum possible overlap and 0 is no overlap). Resampling significance, double cross indicates p-value less than 0.001, that the overlap happened by chance. Within each diagram, from left to right, the bar plots represent overlap between a) thumb and index flexion, b) pinching and thumb flexion, c) pinching and index flexion, and d) pinching and the geometric mean of thumb/index flexion (calculated as the square root of the channel-wise product of significant broadband-related R-squared values between thumb and index).

Disclosures: P. Kerezoudis: None. **M. Jensen:** None. **H. Huang:** None. **J. Rotter:** None. **J.G. Ojemann:** None. **D. Hermes:** None. **K.J. Miller:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.11/FF22

Topic: E.05. Brain-Machine Interface

Support: SFB 295 retune

Title: Phase-dependent neural feedbackrefines closed-loop spinal cord stimulation in animal models of Parkinson's disease

Authors: *E. L. GARULLI[1], B. . KABAOGLU[2], R. DE SA[3], C. G. MCNAMARA[4], M. ENDRES[5], C. HARMS[6], N. WENGER[7];
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Abstract: Epidural Electrical Stimulation (EES) of the spinal cord is a promising therapy that has alleviated gait deficits in animal models and patients with Parkinson's disease (PD). Here, we hypothesised that a closed-loop stimulation, targeted to specific phases of cortical oscillations, can refine the interaction EES with pathological network states. For this, we developed a real-time system that tracks peak-frequency within the beta-band to optimise signal to noise ratio during online phase-tracking. We used this system to deliver high-frequency bursts of stimulation in relation to ECOG signals from M2 cortex. Our results confirmed the presence of network alterations in the unilateral 6-OhDA rat model that were dependent on precise timepoints of stimulation. Experiments in sham animals verified that alterations were specific to neural modulation and not a result of stimulation artefacts. Together, our work provides a tangible solution for the future design of closed-loop stimulation strategies for clinical translation.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.12/FF23

Topic: E.05. Brain-Machine Interface

Title: Using an Orthogonal Neurofeedback Brain Machine Interface to Study the Relationship Between Intracortical High Gamma Activity and Spikes

Authors: *T. LEI[1], M. R. SCHEID[2], J. I. GLASER[2], M. W. SLUTZKY[2];
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Abstract: Local field potentials recorded from the cerebral cortex are derived from a mixture of brain activities, which are reflected in different frequency bands. Among them, the high gamma band is widely considered as a proxy of neuronal ensemble firing. Here, we investigated whether monkeys could dissociate the high gamma and spiking recorded with the same electrode. To do this, we designed an orthogonal neural feedback (ONF) brain machine interface paradigm that

required monkeys to control a cursor by modulating a control channel's spiking activity independently from high gamma activity (HGA) to reach targets in different directions Three macaques could reliably dissociate spiking activity from changes in HGA, with a correlation coefficient dropping from 0.5±0.22 to 0.1±0.13 before and after training. This indicated that high gamma activity is not simply a reflection of local neuronal spiking activity. Further, we sought to understand how HGA and the neuronal population's spiking activity were related. We used factor analysis to investigate how the variance of the individual control channel was shared with the neural population during ONF control, and we found that the shared variances of the spike rates were consistently and significantly lower when the monkeys were solely modulating spikes compared to solely modulating HGA. This result indicated that HGA recorded on a single electrode was correlated with the common co-firing patterns across the neuronal population. This again suggests that HGA is produced not simply by the sum of local neuronal activity, but by the synchrony (co-firing) of multiple neurons across a population. Further, it suggests that neurons can learn to fire independently without the interference of the common co-firing patterns using ONF. This robust relationship between HGA and neuronal population firing helps us further understand the origin of HGA.

Disclosures: T. Lei: None. **M.R. Scheid:** None. **J.I. Glaser:** None. **M.W. Slutzky:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.13/FF24

Topic: E.05. Brain-Machine Interface

Support: NIH Grant 5UH3NS107714-02

Title: Temporal dynamics of sensations evoked through intracortical microstimulation in human brain-computer-interfaces

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Abstract: Brain-computer interfaces (BCIs) aim to improve the quality of life of severely paralyzed people by decoding movement intention from brain signals and translating them into control signals that can be used to control robotic devices. Invasive BCIs can be extended to also provide artificial somatosensory feedback using intracortical microstimulation (ICMS) through electrode arrays implanted into the somatosensory cortex.
Our prior work in humans has shown that ICMS evoked sensations can be reliably localized on the skin surface and that their perceived intensity varies depending on the stimulation

parameters. Further, the reaction times to ICMS are similar to the reaction times from mechanical stimuli. However, it is largely unknown how the temporal acuity of sensations evoked by ICMS compare to natural sensations. In this study, we investigate how the temporal dynamics of the evoked sensations are related to the dynamics of the ICMS trains themselves using a discrimination task. Three male participants with spinal cord injury participated in the study. All three had microelectrode arrays implanted into the hand representation of area 1 in the somatosensory cortex. We presented participants with two stimulation periods (with a fixed duration and stimulus amplitude) that were temporally separated by a pause of varying length. Participants were asked to report whether they felt a single sensation or two distinct sensations separated by a gap between them. The paradigm included both charged-matched and duration-matched control trials.
Surprisingly, we found that the participants often could not perceive even large gaps between stimulus trains – from 0.1 to 0.4 s. Indeed, while some electrodes conferred a high sensitivity to gaps, others did not. These differences could not be explained solely by differences in perceived intensity as changes in stimulation amplitude had only minor effects on discrimination performance. Even for the more acute electrodes, gap sensitivity was far lower than that observed in natural touch or even with electrical activation of peripheral nerves. These results highlight the differences between ICMS-evoked and naturally evoked sensations and suggest that the dynamics of the evoked sensations must be taken into consideration when designing encoding strategies for closed-loop BCI applications.

Disclosures: R. Lienkamper: None. **C.M. Greenspon:** None. **T. Hobbs:** None. **S. Bensmaia:** None. **R. Gaunt:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.14/FF25

Topic: E.05. Brain-Machine Interface

Support: NSF 2137255

Title: A systematic review of implanted brain-computer interfaces for communication and motor control toward a roadmap for surgical brain-computer interfaces

Authors: *M. PATRICK KRUEGER[1], I. T. PAVLIDIS[2], J. L. CONTRERAS-VIDAL, Ph.D.[1]; [1]Electrical and Computer Engin., [2]Natural Sci. and Mathematics, Univ. of Houston, Houston, TX

Abstract: In 1996, PR Kennedy performed the first surgical implantation of electrodes into the brain of a Locked-in-Syndrome patient to demonstrate the feasibility of deploying a Brain-Computer Interface (BCI) system for communication via a neural-controlled cursor, with the first successful usage occurring in 1998. In the following decade, only seven new subjects received either Kennedy's electrodes or Cyberkinetic (now BrainGate) System to drive BCI systems

controlling neuroprosthetics for communication or motor control. Fifteen years after the first successful BCI deployment, the Obama Administration announced a US BRAIN Initiative, with funding initiated in 2014. Since then, the number of surgical BCI research groups has more than doubled, with subjects more than tripling to over 60 who have been implanted. With the BRAIN Initiative's 2025 conclusion concurrent with a profusion of novel devices moving toward marketability, this research provides a detailed assessment of the current implanted BCI landscape for communication and motor control that is needed to illuminate the gaps, missed opportunities, and challenges to enable the forward progression of the field. This in-depth systematic review combining findings from peer-reviewed and grey literature, which are enhanced with interviews of key stakeholders from research groups and device manufacturers, provides a complete summarization of the subjects who have had electrodes implanted, including demographics, etiology, and type of electrodes; the devices used in human subject testing including temporal signal quality and adverse events due to implantation; the communication and motor control experimental protocols carried out; and the composition of research teams. This detailed map spotlights the gaps in BCI research, such as the lack of pediatric applications and regulatory tools; missed opportunities such as data sharing, computational modeling, and reproducibility; and challenges such as interoperability, long-term reliability and prognosis, and ethical prospects for out-of-laboratory usage into clinical and home settings. With human trials starting in 2021 for Synchron and in 2023 for Precision Neuro and Nuralink, with other manufacturers (Paradromics, Blackrock Neurotech, Axoft) having secured FDA Breakthrough Device status, the number of new subjects receiving implants is poised to proliferate in the next decade. To ensure the safety, efficacy, reliability, and translatability of implanted BCI systems, these gaps, missed opportunities, and challenges must be addressed to smooth the transition from experimental to widespread clinical and home usage.

Disclosures: **M. Patrick Krueger:** None. **I.T. Pavlidis:** None. **J.L. Contreras-Vidal:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.15/GG1

Topic: E.05. Brain-Machine Interface

Support: NIH K23NS114190

Title: Beta-band power modulation in the human corticolimbic circuit during arm-reaching movements

Authors: *R. MARTIN DEL CAMPO VERA, A. KAMMEN, J. CAVALERI, Z. GILBERT, R. CHUNG, S. ZHANG, S. SUNDARAM, A. LEONOR, C. LIU, S. KELLIS, B. LEE; Neurolog. Surgery, USC, Los Angeles, CA

Abstract: Recent developments in stereotactic electroencephalography (SEEG) have allowed researchers to study human deep brain areas, such as the corticolimbic system, which is thought to be involved in cognitive control and processing of uncertainty; however, little is known about its role in voluntary movements. This study aims to evaluate differences in spectral power over the beta-band across corticolimbic structures during two different arm-reaching tasks. Ten participants (five female, average age 35) had SEEG electrodes implanted as part of their epilepsy monitoring. These electrodes included the frontal, amygdala, hippocampus, and orbitofrontal cortex (OFC) areas. SEEG data were recorded during two variants of the classic Center-Out arm-reaching task. In the Go/No-Go task, participants were cued to reach a target (Go trials) or withhold movement (No-Go trials) based on a colored cue. In the Always Go task, participants reached a target in all the trials. The Wilcoxon signed-rank test was used to assess significant beta-band power changes with alpha level of 0.05. P-values were adjusted using the Benjamini-Yekutieli procedure to account for multiple comparisons. In the Always Go task, beta-band power significantly decreased during movement, with the frontal and hippocampal areas being the most common to exhibit a significant reduction in power (5 out of 6, and 8 out of 10 participants respectively), followed by the amygdala in 5 out of 10, and OFC in 4 out of 8. In the Go/No-Go task, beta-band power significantly decreased during Go trials and increased during No-Go trials. In Go trials, compared to the Always Go task, the proportion of patients with a significant beta-band power decrease remained unchanged in the hippocampus and OFC, whereas in the rest of the brain areas, the proportion of participants with a significant beta-band power decrease was higher (8 out of 10 in the amygdala, and 6 out of 8 in the OFC). In No-Go trials, the most common area with a significant beta-band power increase was the hippocampus in 8 out of 10 participants, followed by the OFC in 6 out of 8, the amygdala in 7 out of 10, and frontal in 4 out of 6. Measures of beta-band power between No-Go versus Go trials show that motor inhibition and execution modulate in opposite directions. When contrasting the two tasks, the presence of movement uncertainty in the Go/No-Go task can affect the magnitude of beta-band power modulation. The extent of such beta-band power modulation can vary across multiple brain areas in the corticolimbic system, suggesting that each of these areas may have different contributions to motor control.

Disclosures: R. Martin Del Campo Vera: None. **A. Kammen:** None. **J. Cavaleri:** None. **Z. Gilbert:** None. **R. Chung:** None. **S. Zhang:** None. **S. Sundaram:** None. **A. Leonor:** None. **C. Liu:** None. **S. Kellis:** None. **B. Lee:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.16/GG2

Topic: E.05. Brain-Machine Interface

Support: European Unions Horizon 2020 research and innovation programme under grant agreement No 862882 (IN-FET project)

Title: Theoretical limits of a neural interface

Authors: *N. CALCINI, R. JOLIVET;
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Abstract: Great efforts are being made to advance the technology of neural interfaces, with the development of better batteries, wireless sensors, the addition of more recording electrodes, or the application of AI algorithms for decoding neural signals. Regarding decoding, the field has yet to achieve a fundamental breakthrough. Here, we attempt to develop a formal and fundamental understanding of the interaction between *in silico* devices and neural tissue. We start to develop a framework, which allows us to estimate some theoretical limits of neural interfaces, by measuring the limits on information a neural interface can capture from neural signals about its network environment.
To do this, we activate a neural network using a binary stimulus representing an external sensory stimulus comparable to the ones used in go / no-go tasks. The stimulus activates the network, which represents the neural substrate acting as a filter between stimulus and a target population. The output spike trains of such a network are sent to a simulated target population. We then reconstruct the LFP, which is measured by a single point electrode. Finally, we reconstruct the mutual information between the signal captured by the electrode, and the original simulated sensory stimulus.
With this framework, and its modular approach, we pose the foundation for a thorough analysis of the current theoretical limitations of a number of neural interfaces, allowing us to examine a variety of interfaces, and the theoretical limits of their functional integration in a neural circuit.

Disclosures: **N. Calcini:** None. **R. Jolivet:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

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Program #/Poster #: PSTR280.17/GG3

Topic: E.05. Brain-Machine Interface

Support: NIH R01NS112497
NIH UH3NS117944

Title: The Early Feasibility of Recording iEEG and Epileptic Spikes with the Brain Interchange System

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Abstract: The use of implanted pulse generators for neuromodulation has proven to be a promising method for treating neurological disorders. For instance, responsive neural stimulation (RNS) for the control of seizures in epilepsy and deep brain stimulation (DBS) in movement disorders. However, implantable systems face various challenges, including recording only from a small number of brain sites, power management, and limited access to the assessed neural data in a continuous fashion. In this study, we investigated the feasibility of recording neural data from two human subjects with refractory focal epilepsy using a wireless, externally powered, portable bio-signal amplifier, the Brain Interchange (BIC) system (CorTec GMBH, Freiburg Germany). We established a MATLAB/Simulink environment to acquire the neural data at 1kHz from the 32 channels of the BIC system and visualize the captured neural activity in real-time. Afterward, the established environment was subjected to validation in a real-world setting, where the intracranial EEG (iEEG) data was split into two streams and simultaneously recorded using a clinical amplifier and BIC system within the epilepsy monitoring unit (EMU). Subsequently, the raw signal quality and background noise characteristics of each stream were quantified and compared. Although the clinical amplifiers utilizing a cable interface exhibited a significantly better noise floor (<25 dB), the BIC system demonstrated the capability to collect data of comparable quality wirelessly and continuously. The primary distinctions in noise floor between the two systems were predominantly observed above 100 Hz. Furthermore, the recorded data for each stream (BIC vs. Natus Quantum (Natus Medical Incorporated, Wisconsin, USA) and BIC vs. Nihon Kohden (Nihon Kohden Corporation, Tokyo, Japan)) underwent a spike detection analysis, ensuring similar/aligned time segments. The results showed a concordance of over 90% between the two systems. As a result of the BIC system's wireless data transfer capability, we may face losing the packets of data during the transfer process (Packet loss). We estimated the packet loss level of the recording interval for each subject. Moreover, to further investigate the effect of ambient noise on the packet loss, we conducted a series of tests in the lab and the electromagnetically shielded chamber, which revealed that there is a significant difference between the two environments (paired t-test, $p = 0.0090$) with an average of 1.47% packet loss in the lab and 0.74% in the shielded chamber.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.18/GG4

Topic: E.05. Brain-Machine Interface

Title: The Brain Interchange System for recording and stimulation on the sheep cortex: a case study towards functionality and safety of ECoG-based neural implants

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Abstract: Although not yet ubiquitous in modern medicine, fully implantable neural interfaces are at the cusp of becoming a widespread tool in transitional and medical research and ultimately for the development of novel therapeutic strategies to target a variety of neuropsychological disorders. Technical advancements allow to build bi-directional neural interfaces that have (concurrent) sensing and stimulation capabilities which allow for more elaborate approaches via electrical brain stimulation. To further advance the introduction of such implants into the daily clinic landscape, preclinical studies with devices currently under development for human application are mandatory to demonstrate basic requirements for medical use: long-term performance, reliability, and safety. With data and results from a preclinical 25-day functional implantation study in the ovine model (2 female adult sheep), we continue general efforts in the field of neural implants to address these crucial points. The Brain Interchange System (CorTec GmbH, Freiburg) used here is a fully implantable (i.e., no physical wire connection through the skin), bi-directional neural interfacing device equipped with two electrocorticographic (ECoG) electrode arrays implanted bilaterally and subdural to obtain electrophysiological signal from and apply electrical stimulation to the cortical surface. To address long-term performance, functionality, and reliability, we show behavior of signals recorded under different cognitive states and impedances across the implantation period and demonstrate stimulation functionality via single-pulse electrical stimulation potentially to be employed to elicit and record cortico-cortical evoked potentials. To underpin the safety aspects, we demonstrate stability of ECoG array implantation via x-ray imaging at the beginning and end of the implantation period and show outcomes of follow-up examinations and histology findings. In summary, the presented results expand the data available on functional implantation of fully immersible neural interfaces, especially on ECoG-based devices with both recording and stimulation functionality. The data and combination of system features presented here may be the basis to unfold the therapeutic potential especially in first human patients suffering from disorders largely affecting the cerebral cortex such as upper limb stroke and encourage the readiness of these systems for clinical use.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

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Topic: E.05. Brain-Machine Interface

Support: Translational Medical Research Award 2021 from the Leenaards Foundation
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Title: Ecog-based brain computer interface WIMAGINE technology for motor compensation: towards home-use

Authors: O. FAIVRE[1], M. BOSQUET[1], C. GOUJON[4], M. DESCHARLES[5], H. LORACH[6], A. GALVEZ[7], S. KARAKAS[2], C. HARTE[8], J. DEDELLEY[9], P. HECK[9], P. BESSOT[9], J. MURPHY[9], A. WATRIN[9], V. DELATTRE[9], T. AKSENOVA[1], F. MARTEL[1], N. KEIJSERS[10], S. CHABARDES[11], J. BLOCH[12], G. COURTINE[13], F. SAUTER-STARACE[3], ***G. CHARVET**[14];
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Abstract: A clinical Brain Computer Interface (BCI) system for chronic application in daily life is one of the major challenges in the field of neuroprosthetics. Motor controlled-BCIs system aim at providing users with control over upper or lower limb. The major challenge for BCI systems with home use for motor disabled subjects is the ability of recording long term stable neuronal signals, decoding this brain activity in real-time with robustness and precision as well as enabling the most transparent possible use for patients by addressing the issues of portability and ease of use without assistance. The CEA leti Clinatec team has developed a Brain-Computer Interface (BCI) system including the first 64-channel fully-implantable WIMAGINE® device enabling wireless electrocortigrams recording, along with a dedicated decoding software

environment. This WIMAGINE-BCI system has been evaluated in two clinical trials (NCT02550522, NCT04632290) to provide the proof of concept that this technology enables brain control of motor restoration devices in people with spinal cord injuries. In particular, we demonstrated that a tetraplegic patient is able to control a 4-limbs exoskeleton thanks to his brain activity monitoring and decoding [1]. The proof of concept of a brain Spine Interface combining the WIMAGINE system with a spinal cord stimulation therapy enabled a paraplegic patient to regain natural control over the movement of his paralyzed legs, allowing him to stand, walk and climb stairs [2]. The long-term stability of the chronic epidural wireless recorder WIMAGINE was also demonstrated over 5-year period after surgery. This WIMAGINE-BCI technology has therefore been developed to meet the main challenges of a Brain Machine Interface for daily life use, such as the ability to perform a chronic and stable measurement of brain activity as well as the accurate and robust decoding in real time with a reduced latency. We have also developed a new version of the system to make it portable (size divided by 6), with greater energy autonomy (multiplied by 3) and greater measurement precision, with the number of channels per implant transmitted simultaneously multiplied by 2. It has been optimized to enable patients to use it independently, without assistance and in complete safety, as part of their daily activities.
[1] Benabid, Alim Louis, et al. "An exoskeleton controlled by an epidural wireless brain-machine interface in a tetraplegic patient: a proof-of-concept demonstration." *The Lancet Neurology* 18.12 (2019): 1112-1122.
[2] Lorach, Henri, et al. "Walking naturally after spinal cord injury using a brain-spine interface." *Nature* (2023): 1-8.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.20/GG6

Topic: E.05. Brain-Machine Interface

Support: 1R01NS121028-01

Title: Exploring the selectivity of monopolar versus bipolar stimulation of the lateral lumbar spinal cord.

Authors: *G. J. ANSAH[1,3], M. DEL BROCCO[1,3], C. H. GOPINATH[1,3,2], M. K. JANTZ[1,3,4], R. BOSE[1,3,4], S. BHOWMICK[5,6], D. J. WEBER[8,3], S. F. LEMPKA[6,5,7], L. E. FISHER[1,3,2,4]; [2]Physical Med. and Rehabil., [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]Rehabiliation and Neural Engin. Labs, Pittsburgh, PA; [4]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA;

[5]Biointerfaces Inst., [6]Biomed. Engin., [7]Anesthesiol., Univ. of Michigan, Ann Arbor, MI; [8]Mechanical Engin. and Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Lateral spinal cord stimulation has shown promise in evoking somatosensory percepts in the missing limb in people with limb amputation. For prosthetic users, this enables them feel somatosensations with their artificial limbs. However, subjects also report sensation in their residual limb. To limit these unwanted sensations, we evaluated the ability of different stimulation configurations using paddle electrodes to selectively evoke sensations in focal regions of the limb.
In 3 acute feline experiments, we exposed the epidural surface of the spinal cord via a lumbosacral laminectomy. Flexible paddle electrodes with 32 contacts, arranged in a 16 × 2 array, were placed laterally on the lumbar spinal cord and secured under the border of the laminectomy. We placed the rostral end of the paddle at the caudal end of the *L6* vertebrae for animal 1, *L5* for animal 2 and *L4* for animal 3. We delivered monopolar and bipolar stimulations over a current range of 15 - 350 µA. Each stimulus train included 250 biphasic pulses with a 66 µs phase pulse width, and a 33 µs interphase interval. We recorded antidromic compound action potentials (CAPs) in the sciatic and femoral nerves and some of their branches in the ipsilateral hind limb. For each amplitude, we computed the number of nerves that produced CAPs using a stimulation-triggered average of the nerve responses. At threshold (i.e., the minimum amplitude that elicited a CAP) we noted nerves that were recruited as a metric of selectivity. In animal 1, 83% of bipolar electrode pairs selectively recruited nerve branches compared to 75% of monopolar electrodes. Both configurations were primarily selective for the tibial and distal tibial nerve branches. Only 1 caudal electrode recruited any femoral nerve branch activity at threshold using monopolar stimulation, albeit non-selectively. In animal 2, 66% of the bipolar trials and 69% of the monopolar trials were selective at threshold. Monopolar stimulation mostly recruited the distal tibial nerve whereas bipolar stimulation mostly recruited the sural nerve. No femoral branches were selectively recruited at threshold. In animal 3, 65% of all bipolar selective pairs and 70% of all monopolar selective electrodes recruited the saphenous branch of the femoral nerve. The common peroneal nerve was the second most selectively recruited nerve in both configurations. The average amplitude for selectivity with monopolar stimulation was 44 ± 28 µA which was higher than for bipolar stimulation 35 ±16 µA. These results demonstrate our ability to selectively recruit nerve branches, suggesting that we can specifically target regions of the limb innervated by those nerves in restoring sensation for amputees.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.21/GG7

Topic: E.05. Brain-Machine Interface

Support: 1R01NS121028-01

Title: Anatomical organization of the feline lumbar dorsal rootlets and optimization of spinal cord stimulation electrode size for somatosensory neuroprosthetic applications

Authors: *M. DEL BROCCO[1,3], G. ANSAH[1,3], C. GOPINATH[2,3], M. K. JANTZ[1,3,4], R. BOSE[1,3,4], S. BHOWMICK[5,7], D. J. WEBER[8,3], S. F. LEMPKA[5,7,6], L. E. FISHER[2,3,1,4]; [1]Bioengineering, [2]Physical Med. and Rehabil., Univ. of Pittsburgh, Pittsburgh, PA; [3]Rehab Neural Engin. Labs, Univ. of Pittsburgh, Pittsburgh, PA; [4]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [5]Biomed. Engin., [6]Anesthesiol., Univ. of Michigan, Ann Arbor, MI; [7]Biointerfaces Institute, Univ. of Michigan, Ann Arbor, MI; [8]Mechanical Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: A primary drawback of existing lower-limb prostheses is their inability to restore somatosensory feedback. Our lab has shown that epidural spinal cord stimulation (SCS) can generate focal sensations in the distal limbs of amputees. However, these sensations also cover more proximal regions of the residual limb, which may provide distracting information regarding the state of the prosthetic limb. In these studies, stimulation was delivered by commercially available electrodes with large contacts, which may limit their selectivity. Achieving selective stimulation and more focal sensations in the missing limb requires the design and development of new electrodes with better arrangements and smaller contacts. To better understand the target neural anatomy and optimize the design of SCS electrodes, we quantified the functional organization of the lumbar dorsal rootlets (DR) and measured selectivity of SCS using custom epidural electrodes. We performed experiments in three cats. We instrumented sciatic and femoral nerve branches with nerve cuffs, and we measured SCS selectivity by recording antidromic evoked compound action potentials (CAPs) in those nerves. We delivered SCS at L4-L7 spine levels through custom epidural electrodes with varying contact sizing (0.15 mm, 0.5 mm, 1 mm), placed laterally over the cord. We also resected the dura and used hook electrodes to repeat these experiments while stimulating individual DR to quantify their functional organization. We quantified SCS selectivity by the ability to evoke a CAP localized to one peripheral nerve branch while avoiding responses in other branches. The highest percentage of selective responses (80%) was achieved using electrodes with contact sizing of 0.5 mm, followed by contact sizing of 1 mm (69%), and contact sizing of 0.15 mm (62%). The threshold amplitude required to recruit the first nerve was the lowest (37.7 μA) using contact sizing of 0.15 mm, and the highest (50.8 μA) using contact sizing of 1mm. The dynamic range (difference between the threshold amplitude required to recruit the first nerve and the next higher amplitude that recruited other nerves) was similar between contact sizing of 1 mm and 0.15 mm, while it was larger using contact sizing of 0.5 mm. DR stimulation at L6-L7 primarily recruited sciatic branches, while DR stimulation at L4-L5 primarily recruited femoral branches. Rare instances of co-activation of both sciatic and femoral branches were observed during DR stimulation, indicating a somatotopic organization. These results provide important next steps to optimize electrode design for stimulating structures in the spinal cord, with the goal to restore somatosensory feedback.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.22/GG8

Topic: E.05. Brain-Machine Interface

Support: NIH Grant UH3NS120191

Title: Characterizing stability of human motor cortical activity recorded with a stentrode

Authors: *N. CHETTY[1,2], J. BENNETT[4], P. E. YOO[4], A. SAWYER[5], K. KACKER[2], A. DALRYMPLE[2], D. SARMA[2], D. DESPRADEL[2], A. FRY[7], N. Y. HAREL[6], S. MAJIDI[6], R. G. NOGUEIRA[8], J. L. COLLINGER[9], N. L. OPIE[7], D. LACOMIS[8], T. J. OXLEY[4], D. F. PUTRINO[5], D. J. WEBER[2,3];
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Abstract: The Stentrode is a novel endovascular brain-computer interface (BCI) that is implanted within the superior sagittal sinus to record bilaterally from the primary motor cortices. The first-in-human trial in Australia demonstrated computer control and digital communication in four people with severe paralysis due to amyotrophic lateral sclerosis (ALS). An Early Feasibility clinical trial began in the United States (US) in July 2022 at three sites. In order for the Stentrode to be viable long-term, these endovascular electrocorticography (eECoG) signals need to remain stable over time to enable decoding of user intent. Multiple factors could contribute to signal instability and/or loss of BCI functionality in people with ALS, including neuronal degeneration and cortical atrophy, cognitive decline, and device-related failures. Here, we explore the stability of eECoG signals recorded over 5 - 8 months. To date, four participants with severe paralysis have been consented and implanted in the US, three diagnosed with ALS and one with brainstem stroke. Data acquisition and system training with the Stentrode began approximately 7 weeks after implantation. Each testing session begins with recording two-minutes of resting state activity, followed by training or utilization tasks. The offline (non-feedback) training tasks consisted of 5-s (± 1 s) rest periods followed by a 5-s period of movement attempt, in which 5 repetitions of attempted movement occurred. The movements attempted included: both ankles, right ankle, left ankle, right hand, left hand, and both hands. Signal stability was assessed when participants were at rest or during motor attempts. The resting state signals were assessed through the root mean square (RMS) of the signal amplitude in the rest period, band power, and bandwidth. The attempted movements were evaluated using the movement (signal) and rest (noise) intervals for band power, percent change in RMS, and signal to noise ratio over the post-implant follow-up period to date. Band power was assessed in the standard frequency bands: alpha (8 to 13 Hz), beta (13 to 30 Hz), low gamma (30 - 60 Hz), and high gamma (60 - 200 Hz).Results obtained thus far demonstrate that the eECoG signals recorded with the Stentrode are visually stable during the current follow up period (max 8

months to-date). Temporal linear regression will be utilized to formally quantify any changes in slope during the follow-up period. The ongoing early feasibility study will continue to evaluate the signal stability beyond one year.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.23/GG9

Topic: E.05. Brain-Machine Interface

Support: National Institutes of Health (NIH) (UH3NS120191)

Title: Spectral features of endovascular ECoG signals recorded from a Stentrode in the human motor cortex

Authors: *K. KACKER[1], J. BENNETT[5], P. YOO[5], A. SAWYER[6], N. CHETTY[1], A. DALRYMPLE[2], D. SARMA[3], D. DESPRADEL[1], A. FRY[5], N. HAREL[7], S. MAJIDI[8], R. G. NOGUEIRA[9], J. L. COLLINGER[10], N. L. OPIE[11], D. LACOMIS[9], T. J. OXLEY[12], D. F. PUTRINO[8], D. J. WEBER[4];
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Abstract: The Stentrode™ is a novel endovascular brain-computer interface (BCI) technology implanted to measure field potentials, similar to electrocorticography (ECoG), from the primary motor cortex to enable communication after severe paralysis. However, the features of these neural signals have not been fully characterized in humans. Participants with severe paralysis due to amyotrophic lateral sclerosis (ALS) and brainstem stroke have been implanted in pilot clinical trials in Australia (n=4) and the United States (n=4). The first in-human study was conducted in Australia, followed by an ongoing early feasibility study at 3 sites in the United States to evaluate the Stentrode's safety. We aimed to identify robust spectral features for decoding the field potentials. Participants performed motor mapping experiments where they were instructed to attempt moving a specific body segment when prompted. The recorded field potentials were filtered into 3 frequency bands: beta (12-30 Hz), gamma (30-80 Hz), and high gamma (80-200 Hz). For each of the 3 band-limited signals, we calculated the change in root-mean-square voltage (Vrms) between rest and movement epochs, quantifying the percentage change of Vrms movement from rest (termed as modulation depth) for each trial. Principal component analysis (PCA) was used to merge signals that were correlated across channels. We also assessed the signal stability of the Stentrode over a 99-day period, by measuring power of every channel for each frequency band. We investigated the features of the Stentrode signals and identified the spectral characteristics that exhibit strong changes in amplitude between rest and attempted movement conditions. The high gamma frequency band exhibited the strongest modulation depth, showing ~100% increase in signal amplitude between rest and movement epochs. Analysis of somatotopic differences exhibited the strongest depth of modulation in the 'both ankles' and 'right hand' attempted movements. The signal power varied approximately 0.5 dB in the high gamma frequency band over the 99-day period, which signifies high stability of the signal over time. The results of our preliminary analysis of the Stentrode signals indicate that these endovascular neural signals exhibit properties similar to those reported for ECoG-based measures of motor intent.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.24/GG10

Topic: E.05. Brain-Machine Interface

Support: NIH R01 EB027584
ANR-18-NEUC-0002-02

Title: Selective activation of nerve fiber subpopulations with intrafascicular stimulation depends on size of electrode active site

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Abstract: Bioelectronic medicine approaches use modulation of neural activity with peripheral nerve stimulation (PNS) to treat diseases. The selectivity of activating the necessary nerve fibers to get the desired outcome depends on the electrode and its configuration used for charge delivery. The effects of different sizes of the electrode active site on fiber recruitment was investigated using multiple longitudinal intrafascicular electrodes (LIFEs) implanted in the sciatic nerve of rats. Electrode impedance was used to estimate the size of the active site. Selectivity of fiber recruitment was assessed using a 32 channel High-Density surface EMG (HD-sEMG) that provided spatiotemporal information about motor fiber activation (M-waves) of the innervated gastrocnemius lateralis (GL) muscle. Experiments were conducted in adult male Sprague-Dawley rats *(n=4)* under isoflurane anesthesia. 2 to 4 LIFEs *(n=11)* were implanted in the sciatic nerve in the tibial fascicle. Pulse Amplitude was changed from threshold up to 2xthreshold at a pulse width at chronaxie based on the Strength Duration curves for each electrode configuration. Monopolar and bipolar configurations were utilized to deliver stimulus pulse trains at 10Hz for 5 seconds using a custom neurostimulator. Peak to peak amplitude of the

M-waves were used to assess spatiotemporal spread of muscle twitch. A similarity index that showed the magnitude of difference between the amplitude values for each channel for each electrode using monopolar vs bipolar configuration was calculated. A higher index value indicates that there is more difference between the configurations. Results showed that the regions of the muscle activated in bipolar configuration are similar to the regions activated by the electrode with lower impedance (bigger active site) in monopolar configuration, p &lt 0.01. There was a medium effect, $R^2 = 0.062$. This suggests that the fibers activated using the bipolar configuration are predominantly closer to the bigger electrode site because their threshold is smaller. In addition, studies using a computational model of a LIFE inside a fascicle demonstrated that LIFEs with longer electrode sites have lower thresholds for fiber activation. Cumulatively, these findings may provide insight for the design of targeted and selective stimulation strategies for using LIFEs for PNS.

Disclosures: **A. Ortega:** None. **M. Rouhani:** None. **A.K. Thota:** None. **J. Asbee:** None. **L. Regnacq:** None. **Y. Bornat:** None. **F. Kolbl:** None. **L. McPherson:** None. **J. Abbas:** None. **R. Jung:** None.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.25/GG11

Topic: E.05. Brain-Machine Interface

Support: NWO call "Crossover", INTENSE

Title: A real-time neuromorphic brain-to-brain interface for simulation and partial functional replacement of damaged brain regions

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Abstract: The development of effective invasive brain-computer interfaces (BCIs) poses major technological challenges, one of which is the accurate, immediate and meaningful interpretation of recorded signals. In the case of (extracellular) spikes, these are commonly counted in quantized time bins and represented as a continuous variable. This approach inherently results in the loss of vital temporal information . To avoid this problem, spikes should be processed in an event-driven manner, using a spiking neural network (SNN).
We demonstrate the feasibility of a closed-loop brain-to-brain (B2B) interface designed to simulate - and not simply functionally replace - the activity of a cortical area to implement a form of functional restoration in the case of loss of function (e.g. induced by stroke or trauma). We combine real-time spike detection and spike injection into a SNN running on a SpiNNaker neuromorphic platform . By leveraging the massively parallel architecture of this neuromorphic platform, large SNNs can be run at biological timescales. This approach allows for the

immediate processing of spiking activity without the loss of temporal information.
For benchmarking experiments, we designed a multi-layer feedforward SNN with current-based leaky integrated-and-fire (LIF) neurons. An electrophysiology signal simulator (FB128, TDT) was used to generate 64 channels of raw data. By applying a high-pass filter (0.6 - 6 kHz) and thresholding, multi-unit activity (MUA) was detected. For each detection event on a channel, a spike was injected into a corresponding input neuron in the SNN. By varying the number of hidden layers and neurons in each layer, the relationship between roundtrip time and model complexity was assessed. Roundtrip latency was measured as the time between a detected spike and the consequent output spike of the SNN. We show a 7.4 ms roundtrip time for a model with no hidden layers, representing processing time for data filtering, thresholding, network serialization and communication from the workstation PC to SpiNNaker. Additional layers increase roundtrip time in a linear fashion, with 4.06 ms for each layer. Hidden layer population size does not significantly affect roundtrip latency.
We conclude that a SNN running on SpiNNaker hardware achieves low-latency, biologically plausible processing of real-time spiking data, and is suitable for functional simulation of brain activity. Future implementations will focus on partial functional replacement of a cortical area via closed-loop application of a SNN, in vivo electrophysiology and optogenetics.

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PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.26/GG12

Topic: E.05. Brain-Machine Interface

Support: NIH UH3 NS121565
NIH U24 NS113637

Title: Design and demonstration of an investigational research platform for phase-triggered cortical stimulation

Authors: *H. CHO[1,2], M. BUCHHEIT[4], C. A. GKOGKIDIS[4], S. C. CRAMER[5], J. OJEMANN[3,1], J. A. HERRON[3,1];
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Abstract: By considering neural oscillations and their dynamic nature, adaptive stimulation may be more effective in modulating brain connectivity. This greater control over connectivity may

indicate that adaptive stimulation approaches have the potential to better investigate the mechanisms underlying neurological conditions and inform stimulation design, resulting in improved therapeutic outcomes compared to open-loop techniques. With growing advances in sensing and stimulation technologies, there has also been a rising interest in the investigation of closed-loop methods. While such improvements have facilitated the progress of novel stimulation therapies, current clinical systems enable limited exploration of the adaptive stimulation design space. Here, we utilize the OMNI-BIC, an open-source software tool to enable customizable stimulation design with the CorTec Brain Interchange (CorTec GmbH, Freiburg, Germany), an upcoming investigational research device, to perform phase-locked stimulation. We implemented a processing pipeline within the OMNI-BIC to identify signals within a certain frequency band and send stimulation during a specific phase of the target signal. The pipeline incorporated elements, including real-time stimulation artifact mitigation to minimize contamination of neural signals, and a phase-locked loop design to dynamically trigger for more robust stimulation delivery. These signal processing components were included to minimize mistimed and over stimulation that could cause undesired effects. This phase-locked algorithm was then demonstrated within two sheep models to determine the feasibility of performing phase-locked stimulation with the OMNI-BIC. Implanted electrocorticography arrays were employed to record neural activity and deliver stimulation pulses. Collected resting state data was used to inform parameters, such as filter coefficients, target frequency, and trigger threshold. We characterized phase-locked stimulation performance across varying stimulation amplitudes for each animal model. Our findings show the OMNI-BIC and Brain Interchange ecosystem is capable of delivering phase-locked stimulation with limited instances of over stimulation, demonstrating the translatability of the OMNI-BIC from benchtop to clinical conditions. These results also illustrate that the customizability of the OMNI-BIC enables greater design control to develop and assess other phase-triggered stimulation or adaptive neuromodulation paradigms.

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Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.27/GG13

Topic: E.05. Brain-Machine Interface

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Title: Chronic electrocorticography in nonhuman primates by an implantable wireless device for brain-machine interfaces

Authors: *T. YAN[1], K. SUZUKI[2], S. KAMEDA[1], M. MAEDA[3], M. TAKUMA[3], M. HIRATA[1];
[1]Osaka Univ., Suita, Japan; [2]Nihon Kohden Corp., Tokyo, Japan; [3]Astellas Pharma Inc., Tokyo, Japan

Abstract: Introduction: electrocorticography (ECoG) signals have been proposed as a stable, good-quality source for brain-machine interfaces (BMIs), with a higher spatial and temporal resolution than electroencephalogram (EEG). However, long-term implantation may lead to chronic inflammatory reactions and connective tissue encapsulation, resulting in a decline in the signal recording quality. Few studies have reported the effects of the surrounding tissue on signal recording and device functionality thus far. Methods: in this study, we implanted a wireless recording device with a customized 32-electrode-ECoG array subdurally in two macaque monkeys for 15 months. We evaluated the neural activities after stimuli of auditory steady-state response (ASSR) and ketamine injection. We compared acute and chronic results of average root mean square (RMS) voltage and power spectral density (PSD). We also examined the chronic tissue reactions around the electrodes. Results: time-frequency analyses of the acute and chronic phases showed similar oscillation features. After 15 months, the RMS voltage for one monkey remained at approximately 80% from 39.8 μV (SD=5.7) to 32.8 μV (SD=3.5), while PSD showed relatively satisfied results. Histological examination revealed fibrous proliferation on both epidural and subdural sides of the dura mater. Dorsal encapsulation included the newly formed tissue and reactive dura mater, while there were only newly formed tissue in the ventral encapsulation. The average thickness of the dorsal encapsulation (1,760 ± 701 μm) was significantly greater than that on the ventral side (661 ± 339 μm, t-test, $p<0.01$). However, we found no evident of inflammation in the cortex. In addition, we measured the gain factor of the thickened reactive tissue and found that the newly formed ventral fibrous tissue attenuated amplitude of the ECoG signals. Conclusions: This study suggests that subdural ECoG may provide chronic signal recordings for future clinical applications and neuroscience research and highlights the role of reducing the thickness of ventral tissue proliferation in long-term recording performance.

Disclosures: **T. Yan:** None. **K. Suzuki:** A. Employment/Salary (full or part-time):; Nihon Kohden Corporation. **S. Kameda:** None. **M. Maeda:** A. Employment/Salary (full or part-time):; Astellas Pharma Inc. **M. Takuma:** A. Employment/Salary (full or part-time):; Astellas Pharma

Inc. **M. Hirata:** 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.; Masayuki Hirata was the representative researcher of the joint research fund between Osaka University and Astellas Pharma Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Masayuki Hirata owns stock of the start-up company JiMED.

Poster

PSTR280. BCI and Neural Prosthetics: Mechanisms and Applications

Location: WCC Halls A-C

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Program #/Poster #: PSTR280.28/GG14

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01NS123074
CDMRP DM 190663

Title: Beta-adrenergic receptor blockades enable enhanced cortical plasticity at high-intensity vagus nerve stimulation, and provide insight into the mechanism of vns-mediated plasticity

Authors: *C. L. NEIFERT[1,3], J. A. A. ADDO[1,3], T. T. DANAPHONGSE[3], S. PILLAI[3], J. MONTEFALCON[1,3], A. RAZACK[3], M. P. KILGARD[3,2], S. A. HAYS[1,3];
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Abstract: Stroke is a leading cause of long-term disability, with therapies targeting neural plasticity showing promise in supporting recovery. Vagus nerve stimulation (VNS) paired with rehabilitative training has been shown to facilitate recovery of motor function and is linked to structural reorganization of neurons. To inform and improve therapies, studies have developed a systemic understanding of the effect of VNS on structures throughout the brain. Norepinephrine (NE) is critical for VNS-dependent plasticity and recovery, but the dynamics of this relationship are not fully understood. Increasing VNS intensity raises the activity of noradrenergic neurons in the locus coeruleus and increases the activity of NE in the neocortex. However, the degree of VNS-driven cortical plasticity follows an inverted-U function corresponding to increased VNS intensity. This suggests a plasticity-stabilizing effect of high NE activity in the cortex. Identifying the contribution of NE to VNS-dependent plasticity holds promise to guide further improvements of VNS-driven therapies.
The goal of this study is to determine the role of adrenergic receptors in VNS-mediated plasticity. The primary hypothesis of this proposal is that β-adrenergic receptors (β-ARs) are critical for modulating VNS-dependent plasticity, and that β-ARs can be manipulated to enhance this plasticity. To test this hypothesis, rats performed a simple behavioral task in which VNS was paired with jaw muscle activation during chewing. For five days, each rat received 200 pairings of VNS delivered at a frequency of 30Hz, at varying intensities and with or without a β-blocker

drug injection. 8 groups were defined by combinations of the following drug and intensity parameters: injection of Propranolol or saline Vehicle injections; and VNS at 1.6 mA (High VNS), 0.8 mA (Moderate VNS), or Sham stimulation. Two additional groups received Atenolol injections with 1.6 mA VNS or Sham treatment. Following each animal's final behavioral session, intracortical microstimulation (ICMS) was used to assess movement representations in the motor cortex.
Preliminary results have shown that High VNS administered with Propranolol produce greater levels of VNS-driven plasticity than our group has ever reported. This suggests that β-ARs are a limiting factor of VNS efficacy, and that blocking β-ARs may further improve VNS therapeutic strategies. This study further elucidates the neuromodulatory mechanism of VNS-mediated plasticity and will form the basis for pharmacologically-augmented VNS therapy to improve post-stroke recovery.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

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Program #/Poster #: PSTR281.01/GG15

Topic: E.06. Posture and Gait

Support: NINDS 1R01NS129576-01A1
NSERC-PDF
Case Western Reserve University School of Medicine

Title: Cortical representation of inertial load during locomotion in the mouse

Authors: *E. KIRK, K. HOPE, B. SAUERBREI;
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Abstract: While the basic locomotor rhythm in rodents is produced by a spinal central pattern generator (CPG), walking in complex natural environments demands continual adjustment of muscle activity to compensate for changes in mechanical load, and is thought to require coordinated interactions across spinal, cortical, and cerebellar networks. Studies of voluntary arm movement in primates have shown the motor cortex generates commands to counteract inertial loads, and these commands are shaped, in part, by ascending cerebellar input. By contrast, cortical dynamics during load compensation in rhythmic, CPG-driven behaviors such as rodent locomotion remain largely unexplored. Here, we use three dimensional motion tracking, electromyography (EMG), neural ensemble recordings, and optogenetics to identify a neural

representation of inertial load in the motor cortex of unrestrained, locomoting mice, and demonstrate that this representation is robust to cerebellar perturbation. Mice were trained to trot on a linear treadmill as 0.5 g weights were attached to the wrist. The wrist weight induced an increase in biceps EMG during swing, consistent with an increase in elbow flexor torque to accelerate the loaded limb. This response was not abolished following suppression of cerebellar output by optogenetic stimulation of Purkinje cells. Next, cortical activity was recorded using silicon probes chronically implanted in the forelimb motor area (n = 558 neurons). A large number of cells were load-responsive (47%), exhibiting both firing rate increases (45% of responsive neurons) and decreases (55%). Responses to cerebellar perturbation were common (28%), and usually consisted of firing rate increases (71% of responsive neurons). At the population level, demixed principal component analysis revealed significant effects of load and cerebellar perturbation, which accounted for 24% and 11% of the explained firing rate variance, respectively. Strikingly, load-related activity was not strongly modulated by step phase, but consisted of a tonic shift. Furthermore, neural activity along load-related dimensions was not grouped by cerebellar perturbation, the interaction between load and cerebellar perturbation was small (1.1%), and the projection of firing rates aligned to stimulation onto load dimensions revealed a minimal response. This cerebellum-independent representation of load might enable cortical dynamics to evolve from an appropriate initial condition when a voluntary, cortically-dependent action must be coordinated with an ongoing, rhythmic, spinally-generated program.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.02/GG16

Topic: E.06. Posture and Gait

Support: NIA R03 AG060290–01
NIA P30 2P30AG028747

Title: Balance perturbation training with a simultaneous cognitive task in older adults: a pilot study

Authors: *N. ALISSA[1], K. P. WESTLAKE[2];
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Abstract: Background: Older adults display a greater tendency to use the reach-to-grasp strategy and a greater frequency of grasping errors. Age-related declines in attention shifting between working memory processes (cognitive task and balance response) may underlie this reduced grasp accuracy in older adults. Compared to older adult non-fallers, older adult fallers display increased movement time and markedly increased grasp error frequency under non-

spatial working memory conditions. This difference between older adult fallers and non-fallers suggests deficits in cognitive shifting ability beyond that which is observed in healthy aging. **Objective:** To investigate the feasibility of a dual task cognitive and balance perturbation reach-to-grasp training intervention in older adults. **Methods:** The 3-day intervention included 15 forward-backward stance perturbations and 15 right-left stance perturbations with a cognitive task. Assessments were conducted using the ActiveStep treadmill, which can deliver customized slip-like balance perturbations. Participants were assessed pre- and post-intervention under 2 testing conditions: a stance slip with a cognitive task in the presence of a handrail, and a walking slip with a cognitive task in the absence of a handrail. The post-intervention assessment also included a third condition: a walking slip with the handrail on the non-dominant side. We calculated in-task falls incidence during each of these conditions using a load cell attached to the safety harness on the treadmill. **Results:** We found reduced in-task falls incidence during slip-like balance perturbations with a secondary cognitive task in older adults after 3-days of perturbation training under the first two testing conditions. During the third condition with the rail on the non-dominant side, we found that participants relied on harness assist, but there were no in-task falls. **Conclusions:** Reduced in-task falls incidence during stance slips with a cognitive task indicates that this training intervention is feasible and effective in older adults. Reduced in-task falls incidence during walking slips without the handrail indicates that although we are training the grasp response, there is no negative effect on the balance response in the absence of a handrail. Our results also suggest that this training effect may generalize to the non-dominant arm.

Disclosures: N. Alissa: None. **K.P. Westlake:** None.

Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.03/GG17

Topic: E.06. Posture and Gait

Title: Flexible and rapid modulation of gait control assessed by long-range autocorrelations

Authors: *C. VANDAMME[1], V. OTLET[2], R. RONSSE[2], F. CREVECOEUR[1];
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Abstract: Gait, as many other physiological signals, possesses a complex temporal organization. Indeed, the fluctuations from one stride to another, originally considered as random noise, display long-range autocorrelations (LRA), meaning that the stride interval at any given time statistically depends on previous gait cycles. Previous works suggested that this feature may result from a selective regulation of stride length and duration while maintaining a target speed. In this framework, it has been suggested that constraining the stride time with a metronome impedes the flexible regulation of this gait parameter, leading to a deterioration of the autocorrelation function of series of stride durations. However, transitions between walking with

and without a metronome (and vice-versa) have not been measured, it is therefore unclear how people adapt to such a change of task. To investigate this, 18 healthy participants were asked to walk overground and synchronise one foot with an isochronous metronome set to their average spontaneous pace, measured prior to the testing involving the metronome. Each participant performed two conditions of 15 minutes in which the metronome was activated during either the first or second half of the session to test both transitions. The fractal exponent, reflecting the level of LRA, was computed with the adaptive fractal analysis (AFA). This method was applied on successive overlapping subsets of the stride series to outline the evolution of the fractal exponent. Results showed a clear transition in both conditions, with LRA of the series of stride duration gradually reduced when the metronome was turned on (difference in fractal exponent of -0.36 +/- 0.14, $P < 0.001$) and recovered when it was turned off (difference of 0.35 +/- 0.14, $P < 0.001$). The same transitions could be reproduced in a model within the framework of stochastic optimal control by an instantaneous change of the parameter linked to the regulation of stride time. Importantly, no significant difference in the standard deviation of stride series was observed between the parts of the series with and without the metronome. The LRA is therefore an essential metric to discern the behavioral properties of paced and spontaneous conditions. Together, our results validate the hypothesis that LRA emerge from a flexible control that rapidly regulates timing and amplitude parameters according to task requirements. In particular, the reemergence of LRA shortly after turning off the metronome establishes it as a robust marker of a meaningful and natural gait behavior.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

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Program #/Poster #: PSTR281.04/GG18

Topic: E.06. Posture and Gait

Title: Motor Adaptation to Stance Slips among Healthy Young Adults: Associations Between Cortical Changes and Reactive Stability.

Authors: *R. PUROHIT[1], J. PITTS[1], S. WANG[1], J. FUNG[2], T. BHATT[1];
[1]Physical Therapy, Univ. of Illinois at Chicago, Chicago, IL; [2]Physical Therapy and Occup. Therapy, McGill Univ., Montreal, QC, Canada

Abstract: Background: Extensive neuroimaging evidence indicates the role of the cerebral cortex in human reactive balance control. Specifically, electroencephalography (EEG) studies have identified that cortical beta frequencies (13-30Hz) reflect sensorimotor processing of perturbations and possibly planning of balance responses (e.g., stepping). Sensorimotor beta power increases with perturbation intensity and is higher in individuals with lower balance ability. Additionally, frontal beta power is shown to increase in challenging postural conditions or in the presence of environmental constraints. However, it is still unclear how the cortical

control of balance is modulated as motor adaptation occurs. Thus, we examined changes in sensorimotor and frontal beta frequencies over repeated stance slips in healthy young adults. **Methods:** Twenty young adults (12 female; ages 18-35) were exposed to twelve stance slips (distance= 0.18 m, velocity=1.36 m/s, acceleration=11.35 m/s^2). Cortical activities were recorded using a 32-channel EEG device with an in-built low pass filter of 500Hz. Using single-trial analysis, beta power was extracted during two time-bins: pre-perturbation (400ms before slip onset) and post-perturbation (400ms after slip onset), focused over frontal (Fz) and sensorimotor (Cz) areas with baseline corrected (using first 200ms of trial). Kinematic variables including center of mass (COM) stability at recovery limb liftoff and touchdown were also assessed. A 2×2×3 ANOVA was used to test the effect of perturbation (pre vs post), cortical area (Cz vs Fz), and trial (S1 vs S6 vs S12) on beta power. A simple linear regression was used to test the correlation between beta power and COM stability. **Results:** There was a main effect of trial on beta power *($p<0.05$),* and post-hoc comparisons showed reduced power at Cz and Fz during both time-bins at S6 compared to S1 *($p<0.05$).* There were no significant changes in beta power between S6 and S12 *($p>0.05$).* There were no other main effects or interactions on beta power *($p>0.05$).* There was a negative correlation between post-perturbation frontal beta power and COM stability at liftoff *($R^2= 0.35$, $p<0.05$).***Conclusion:** Healthy young adults demonstrate reduced sensorimotor and frontal cortical beta power with motor adaptation, suggesting reduced engagement of or reliance on the cerebral cortex for balance recovery. Further, individuals with lower reactive stability demonstrated higher frontal beta power, suggesting higher demand of cognitive resources for subsequent balance recovery. Over repeated perturbations, individuals may rely less on the cortex for sensorimotor processing and response planning.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

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Program #/Poster #: PSTR281.05/GG19

Topic: E.06. Posture and Gait

Support: Project was supported by institutional start-up and capital funds allocated to P. Ledwidge, J. Kadlowec, and A. Morgan

Title: The N200 event-related potential correlate of cognitive-motor interference in ACL-reconstructed athletes: preliminary findings

Authors: H. COSTLOW[1], R. GUGGENHEIM[1], J. BLANKENBURG[1], J. PETRUS[1], A. JOHNSON[1], J. ABT[2], J. CALCEI[3,4], J. VOOS[3,4], J. POLOUSKY[5], M. MORSCHER[5], A. MONTGOMERY[1], J. KADLOWEC[1], A. MORGAN[1], ***P. LEDWIDGE**[1,6];
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Abstract: Anterior cruciate ligament (ACL) injuries are most common in athletes in pivoting/cutting sports. One in four young athletes who return to sport (RTS) after ACL reconstruction will incur a second ACL injury. This suggests current criteria for RTS decision making may be missing underlying factors that contribute to secondary ACL injuries. The goal of this confirmatory study was to establish whether ACL-reconstructed athletes experience deficits in how they allocate limited-capacity neural resources between concurrent cognitive and neuromuscular tasks (*cognitive-motor interference*). Participants were ACL-reconstructed athletes who returned to sport (n = 8) and non-injured controls (n = 6) matched by sport, age (M = 21, SD = 1.1 years), sex, body mass index, and leg dominance. All research procedures were IRB-approved and aligned with the Declaration of Helsinki. The N200 event-related potential (ERP) component, a neural correlate of cognitive-motor interference, was recorded using 128-electrode EEG during the Flanker task while participants were seated (single task) and balancing on their reconstructed/matched limb (dual task). Participants completed eight randomized blocks of 16 Flanker trials (50% incongruent) in single-task and dual-task conditions. ERPs were stimulus-locked and averaged within four bins per participant: congruent and incongruent trials in single- and dual-tasks. The N200 was measured per bin as the mean amplitude of the difference wave (incongruent minus congruent) between 250-378 ms at FCz. Towards ensuring scientific rigor, data processing (EEGLAB/ERPLAB) occurred blind to group membership, appropriate matched controls were tested, a temporal principal components analysis derived an unbiased time window for the N200, and effect sizes and confidence intervals are reported. Results from a 2 (single, dual) x 2 (ACL, Control) mixed ANOVA indicated that the N200 was more negative for the ACL group than Controls, $F(1,12) = 5.50$, $p = .037$, $d = 1.27$ (95% CI = 0.11, 2.42), which was explained by this effect in the dual-task only, $F(1,12) = 6.64$, $p = .024$, $d = 1.39$ (95% CI = 0.21, 2.57). These results suggest that ACL-reconstructed athletes are more likely to allocate greater cognitive-control resources to their visual-cognitive environment than non-injured controls during dual-tasks. ACL-reconstructed athletes may experience neuroplastic changes in how they manage multi-task cognitive-motor environments, such as during sport. These preliminary findings support further evaluation as to how neuroplasticity may be involved in risk for second ACL injury.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.06/GG20

Topic: E.06. Posture and Gait

Support: NIH R01 HD46922 (L.H.T.)

Title: Cortical responses in modern dancers are more sensitive to balance perturbation but reflect more automatic balance control than nondancers

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Abstract: Cortical engagement during whole body movements such as walking and balance can augment ongoing subcortical processes as necessitated on an individual basis by task difficulty and ability. Individuals with worse balance exhibit increased cortical activity during balance recovery, but how this engagement varies with expertise is unclear. Typically, tasks require less cortical engagement with expertise. However, this has not been clearly demonstrated in individuals with highly trained balance skill such as dancers. We hypothesized that professional modern dancers require less cortical engagement during reactive balance than nondancers due to their fine-tuned sensorimotor integration and balance ability. After assessing balance ability via a difficult beam walking task, we recorded electroencephalography (EEG) in 11 healthy young adults, 6 nondancers (2F) and 5 dancers (5F) throughout recovery from support surface balance perturbations at two magnitudes that involved a single balance-correcting step. We assessed two metrics of cortical engagement from the Cz electrode: the cortical N1, an index of error assessment that peaks 100-150 ms post-perturbation, and sensorimotor beta power (β; 13-30Hz oscillations), an index of sensorimotor integration known to decrease after the N1 and prior to voluntary movement. The N1 is localized to the supplementary motor area and is larger in nondancers with worse balance ability. We predicted smaller N1 amplitudes and smaller decreases in perturbation-evoked β during balance recovery in dancers compared to nondancers. In line with previous studies, N1 amplitudes increased with perturbation difficulty in both cohorts. Contrary to our hypothesis, there was a trend for larger N1 amplitudes in dancers compared to nondancers, indicating dancers are more sensitive to balance error potentially due to training in detecting disturbances to body posture. Dancers also had higher balance ability scores, suggesting the N1 may not directly reflect balance ability but rather individual sensitivity to balance errors. Following the N1 response, β power decreased in all participants, presumably reflecting cortical engagement for a balance correcting step. β power tended to decrease less in dancers, suggesting dancer balance recovery is more automatic. These findings may improve our understanding of the mechanisms of balance control that can facilitate the development of individualized balance training interventions to reduce falls risk.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.07/HH1

Topic: E.06. Posture and Gait

Title: Manual balancing of a visual inverted pendulum by quantized versus proportional joystick commands

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Abstract: OBJECTIVE: Manually balancing a visual inverted pendulum (VIP) with a joystick is a learned skill which exhibits drift and intermittent corrections, analogous to the sway and proportional ballistic corrections seen when the ankles are used for bipedal balancing. This study aimed to compare VIP balancing when commands are discretized versus proportional to joystick deflections. **METHODS**: A beam and bob display pivoted about its fixed base with inverted pendulum dynamics ($\ddot{\Theta}=K_P \sin\Theta$) driven by joystick commands. K_P was set to create an intrinsic frequency of .46 Hz, similar to postural sway. Two groups of 9 subjects were instructed to keep the VIP upright and as stable as possible and to avoid ±60° boundaries which defined a "fall". For the "P" group, VIP acceleration was proportional to joystick deflection times 0 .28 rad/s^2; For the "D" group, a discrete acceleration of .28 rad/s^2 was issued whenever joystick deflection exceeded ±1°. Every subject completed 30 trials in their assigned command mode plus a catch trial of the other type every 10 trials. **RESULTS:** The D group fell significantly more in their first 10 trials than the P group. Both groups showed significant fall reduction across trials, but the D group ended with significantly more falls than the P group. The RMS angular displacement and velocity of the VIP were also significantly higher for the D than the P group, across all trials. The first catch trial of each type was indistinguishable from the 10th main trial of its type, and the number of falls declined significantly across both types of catch trials. However, the final number of falls was greater for catch trials than for main trials of the corresponding type. The decline in falling among main and catch trials of both types was correlated with growth of the intervals between commands. In 18% of joystick deflections during the first 10 trials both groups made destabilizing commands which accelerated the VIP toward the fall boundary it was approaching, and both groups showed significantly fewer destabilizing deflections over trials. **CONCLUSION**: In this balancing task, proportional control improves performance by decreasing drift and improving the success of serial ballistic corrections when falls were imminent. However, VIP balancing can be learned without proportional control. The transfer of learning to catch trials indicates a common mode of learning for discrete and proportional control. In both control modes, the timing and duration of serial ballistic commands improved, and frankly destabilizing commands which are seen when falls are imminent declined. These results inform the modeling of human behavior in this task, e.g., with machine learning.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

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Program #/Poster #: PSTR281.08/HH2

Topic: E.06. Posture and Gait

Support: Work supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)

Title: The neural bases of sensory reweighting for postural control: a neuro-computational model

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Abstract: Sensory reweighting (SR) involves integrating sensory inputs from various sensory sources, including vision, proprioception, and the vestibular system. The importance of SR lies in its ability to adaptively adjust the contributions of these sensory inputs based on their reliability and relevance in a given context, thus allowing the body to respond effectively to changing environmental conditions and sudden disturbances. Understanding SR can lead to advancements in rehabilitation for individuals with balance disorders. Although SR is considered crucial for postural control, the neural mechanisms underlying this process remain unclear. Existing computational models used to investigate SR are mainly "black-box" models. While these models can replicate the behavior of the brain, they do not explain why and how this is happening in the real brain. To fill this gap in the literature, in this work we use a classical biologically plausible neuro-computational model of multisensory integration, to elucidate the neural mechanisms at play in the sensory organization test (SOT), a widely utilized experimental protocol for investigating SR. Considering that the plastic remodeling in the nervous system occurs at a significantly slower temporal scale compared to SR, we put forth the hypothesis that there is no actual reweighting process taking place. Instead, we propose that the adaptive adjustments in the contribution of each sensory modality can be explained by the process of multisensory integration (MSI). In particular, we investigated two alternative hypotheses to explain the empirical findings in the literature: 1) the six conditions observed in the SOT can be attributed to a reweighting process, and the synaptic weights of each sensory modality adapt based on the amount of information contributed by that modality in a given situation; 2) the variations in the six SOT conditions are solely due to differences in the reliability of the stimuli and the MSI operation, without any reweighting process occurring. Our findings provide evidence that the SR theory cannot account for all six SOT conditions, while the MSI does, confirming the starting hypothesis. Additionally, the model is capable of explaining how these neural mechanisms are altered in different clinical populations (e.g., vestibular patients and autistic individuals). We will further validate the proposed model with newly collected experimental data, by analyzing the effect of incrementally varying visual and proprioceptive inputs on both model results and center of pressure-based postural sway measures.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.09/HH3

Topic: E.06. Posture and Gait

Title: Aging alters dual-task resource allocation during concurrent speech comprehension and dexterous balancing tasks

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Abstract: Objective: Older adults tend to "stop walking when talking," a well-documented phenomenon associated with increased risk of falling. We sought to examine the allocation of cognitive resources during concurrent speech comprehension and manual balancing. We designed an animated visual inverted pendulum (VIP) balancing task similar to the experience of balancing a pencil on one's finger. With no feedback between a joystick interface and VIP displacement, we can isolate engagement of high-level oscillatory dynamics by circumventing biomechanical and reflexive levels of control which cannot be eliminated in real gait and posture tasks. **Methods**: Participants were 20 younger (YA; 18-31 years) and 20 older (OA; 62-81) adults, all healthy and with clinically normal hearing (PTA < 25dB). For the listening task, participants indicated whether the agent of an action was the same or different in sequential pairs of sentences with subject-relative and object-relative clause structures. For the balancing task, participants attempted to balance a VIP shown on a computer monitor via lateral deflections of a joystick; a "fall" was counted if VIP displacement exceeded ±90° from the center position. Easy and hard versions of the listening and VIP tasks corresponded, respectively, to different sound levels and pendulum acceleration constants. Participants completed 8 counterbalanced conditions: single- and dual-tasks in all combinations of task type and difficulty. **Results**: OA performed significantly ($p<.05$) worse on both tasks (i.e., increased VIP falls and comprehension errors) compared to YA across all difficulty levels. In both single- and dual-task conditions, all participants performed worse on the VIP task as difficulty increased. Dual-tasking impaired OA VIP performance but not speech comprehension as compared to single-task conditions. Dual-tasking impaired YA VIP performance and comprehension relative to single-tasking when both VIP and comprehension tasks were more difficult. **Conclusion**: YA showed dual-task degradation in both balancing and listening when both tasks were more difficult, indicating sharing of central processing resources which is not offset by prioritization of one task over the other. OA showed worse overall performance and steeper dual-task deficits in balancing than YA and no dual-task deficits in listening, suggesting prioritization of speech comprehension over potential resource interference. It remains to be seen 1) if VIP balancing and real bipedal balance share resources in a dual-task paradigm and 2) if OA still prioritize listening in a real postural task where falling has a high cost.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

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Program #/Poster #: PSTR281.10/HH4

Topic: E.06. Posture and Gait

Title: Reinforcement feedback leads to greater motor exploration during gait

Authors: *J. JEKA[1], J. GRAY[1], A. ROTH[2], J. BUGGEIN[3], H. REIMANN[2], J. CASHABACK[2];
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Abstract: Introduction: Error-based feedback is typically thought to play the dominant role in learning a new movement pattern. However, recent work has underscored how reinforcement (success/fail) feedback may play a critical role as well. During reaching we have recently shown that a lack of reinforcement (failure) causes greater variability and positive reinforcement (success) updates the intended motor action towards the last success, leading to greater spatial exploration of the solution space. Here we investigated the roles and interplay of reinforcement and error feedback on motor exploration while walking. **Methods:** Six healthy young subjects (age 22-26, 3m, 3f) walked on a instrumented treadmill with a 180º virtual reality screen showing an endless path of randomly generated flowing cubes. Subjects were instructed to match a target step length created from their baseline left step length plus 2 standard deviations in 3 conditions. Error feedback displayed their left foot step length as a horizontal line relative to a target left foot step length. Reinforcement feedback showed a gray target that would turn blue when their left foot step length was within the target boundary. Subjects did not have knowledge of the error magnitude during reinforcement, only hit/miss. Both types of feedback were simultaneously shown in the combined condition. Lag-1 autocorrelations of the step length were calculated for each condition. A greater lag-1 autocorrelation represents a greater level of exploratory behavior during the walking task.**Results:** Left step length was compared to the target step length on each step. A bootstrapped hypothesis test on the paired differences showed that the reinforcement feedback led to greater motor exploration during walking (i.e., a higher lag-1 autocorrelation).**Conclusions:** Preliminary results from our step length modulation paradigm provide promising evidence that exploration is a generalizable mechanism across reaching and gait, which can be used to adapt and potentially learn new movement patterns. Further study will help to understand the ways in which the upper and lower limb tasks may differ as well as investigating the neuroanatomical input to motor adaptation with basal ganglia impairments due to Parkinson's Disease.

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Poster

PSTR281. Posture and Gait: Supraspinal Control

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Program #/Poster #: PSTR281.11/HH5

Topic: E.06. Posture and Gait

Support: National Institute on Aging Grant (R21AG075489)

Title: Posterior parietal cortex activity during visually perturbed gait

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Abstract: Real-world gait is complex, often requiring step adjustments to meet environmental demands. Poor gait performance, especially during perturbed gait conditions, is related to increased fall risk and mortality in older adults. Increased cortical activity has been identified during gait in older adults, however evidence is limited to frontal cortex regions during unperturbed gait. Quantifying activity in the posterior parietal cortex (PPC; critical for sensorimotor integration) during perturbed gait is an essential step toward understanding cortical mechanisms of gait impairment in older adults. The purpose of this preliminary study is to quantify PPC activity changes in healthy young adults during unperturbed and perturbed gait conditions. We present preliminary data from five young adults (mean age 23.0[2.1]yrs, 2 female). PPC activity was quantified using functional near-infrared spectroscopy, which uses near-infrared light to quantify changes in deoxygenated and oxygenated hemoglobin (HbO2) concentrations. Participants completed three, 3-minute treadmill gait conditions at their preferred speed: regular walking, visually cued walking, and visually cued walking with step adjustments (perturbed gait). For visually cued conditions, illuminated rectangular stepping targets, adjusted to the participant's foot size, were projected onto the treadmill belt's surface, and approached the participant at belt speed. The anterior–posterior (AP) and lateral distances between stepping targets were attuned to the participant's preferred step length and width, respectively. Step adjustments were imposed by random target perturbations in the AP or lateral direction, occurring once the approaching target came within 130% of step length from the participant. No significant differences in PPC HbO2 concentration changes were observed across gait conditions, however a moderate Cohen's *d* effect size was observed for change in HbO2 concentration between the two visually cued conditions ($t(4) = -1..53$, $p = 0.2$, $d = -0.69$), suggesting increased PPC activity where step adjustments were necessary. A small effect size was observed for increased PPC activity during visually cued as compared to regular walking ($t(4) = -0.54$, $p = 0.62$, $d = -0.24$). Considering our small sample in this preliminary study, these findings hold promise for larger effects in older adults. We will expand on these results by increasing the sample size and testing older adults with and without a fall history. Elucidating the role of the PPC in complex gait performance and fall prediction will better inform the development of neuromotor-based fall interventions.

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Poster

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Topic: E.06. Posture and Gait

Support: NIH Brain Initiative Grant F32MH122995

Title: Cortical encoding of full-body posture and movement in freely-behaving mice

Authors: K. S. SEVERSON[1], J. LU[1], ***H. JIANG**[2], W. XIAO[1,3], S. CHOI[1], T. W. DUNN[4,5], F. WANG[1];
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Abstract: The brain's internal representation of the spatial configuration of the body is called the "body schema." The body schema arises in higher-order cortical regions and is updated using proprioceptive and other sensory information originating in peripheral tissues. Neural activity correlated with body posture has been observed in higher-order cortical areas in primates and rodents, such as posterior parietal and secondary motor cortices, yet the circuit and network dynamical mechanisms underlying how proprioceptive information in the somatosensory cortex is integrated into the body schema remains is not well understood. Here, we investigated the sensory origins of body schema in the somatosensory cortex of freely-moving mice by recording simultaneous large-scale electrophysiological and 3D-calibrated multi-camera recordings. Full-body postures and movement were tracked by recording freely behaving mice with six synchronized cameras and utilizing DANNCE, a markerless 3D pose estimation tool. We then used geometric models to extract Euler angles for 16 major joints from the 44 3D-tracked keypoint positions. This set of joint angles thus parameterizes full-body posture, allowing for detailed analysis into how various postural, movement, and spatial features are encoded in single-unit electrophysiological activity recorded using 64-channel tetrode microdrives chronically implanted in either S1 dysgranular zone (S1dz), S1-M1 transition zone (S1tz), secondary somatosensory cortex (S2), or posterior parietal cortex (PPC). Tuning to joint angles was strongest in PPC and S1tz, weaker in S1dz, and weakest in S2. While neurons in S1tz, PPC, S1dz, and S2 showed relatively weak correlations with specific joint velocities at fast timescales, neuronal ensembles in these regions were modulated by brain states associated with non-specific movement on longer timescales. Finally, PPC neurons showed stronger tuning to features in spherical coordinates than somatosensory regions, suggesting a joint-centered reference frame present in early somatosensory regions may be transformed into a body-centered spatial reference frame in PPC, a known component of the body schema network. Thus, advances in full-body pose tracking enable deeper investigation into complex posture and movement

representations, which lay a foundation to study mechanisms underlying body schema and the neural control of posture and movement.

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Poster

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Title: Frequency-domain patterns in foot-force line-of-action: an emergent property of standing balance control

Authors: *R. SUGIMOTO DIMITROVA[1], K. SHIOZAWA[1], K. G. GRUBEN[2], N. HOGAN[1]; [1]MIT, Cambridge, MA; [2]Univ. Wisconsin, Univ. Wisconsin, Madison, WI

Abstract: Despite over half a century of studies on human standing balance, the underlying controller responsible for stably maintaining our center of mass high above our two feet remains elusive. Quiet standing studies are particularly appealing, as they allow for observations of natural, unperturbed stance. A metric that could capture aspects of quiet-standing-balance dynamics and control would be useful for understanding the underlying control mechanisms, and will also facilitate diagnosis of impairments and tracking recovery. A recent line of work suggests that the net behavior of the foot-ground interaction force provides insight into quiet-standing-balance dynamics and control. Through human subject experiments, Boehm et al. uncovered that the relative variations in the center of pressure and force direction emerge as a distinct pattern in the frequency domain, and through numerical analysis, Shiozawa et al. showed that different control strategies are reflected in the frequency-domain patterns. In this work, we develop a spectral-based approach to analytically predict the expected frequency-domain curve (reflecting the foot-force behavior) from any linear model of standing that gives as output the center of pressure and foot-force direction. The analytic method confirms that the metric depends on the controller and physiological noise, and not just mechanics. Furthermore, the method facilitates validation of mathematical models by providing fast and sure metric prediction to compare with experimental measurements. Finally, the analytic expression explains the sensitivity of the metric to different model parameters such as noise strength and noise dynamics, thereby allowing us to better interpret the metric, its strengths, and its limitations. As such, the

analytical description of the emergent foot-force behavior developed in this work further supports the utility of this metric in probing the quiet-standing-balance controller.

References

Boehm, W. L., Nichols, K. M., and Gruben, K. G. (2019). Frequency-dependent contributions of sagittal-plane foot force to upright human standing. *Journal of Biomechanics*, *83*, 305-309. https://doi.org/10.1016/j.jbiomech.2018.11.039 Shiozawa, K., Lee, J., Russo, M., Sternad, D., and Hogan, N. (2021). Frequency-dependent force direction elucidates neural control of balance. *Journal of NeuroEngineering and Rehabilitation*, *18*(1), 145. https://doi.org/10.1186/s12984-021-00907-2

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Poster

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Support: NIH-R37-HD087089
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Title: Human Foot Force Informs Neural Control Strategies of Quiet Balance

Authors: *K. SHIOZAWA[1], M. RUSSO[2], J. LEE[1], N. HOGAN[1], D. STERNAD[3];
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[3]Northeastern Univ., Boston, MA

Abstract: Despite the abundance of studies identifying the dynamics of perturbed human balance, understanding the control mechanisms of quiet standing has been difficult. Furthermore, although the ground reaction force is often measured to determine balance ability in subjects, only its vertical component and its point of application, i.e., the center of pressure, are usually considered. While the vertical component of the force dwarfs the shear component, the vertical force alone cannot achieve stable balance and the horizontal force is essential to provide translational stability. Previous work identified a point of intersection of ground reaction forces that combines the information from center of pressure with force direction. This intersection point exhibited consistent frequency-dependent behavior during quiet standing across multiple subjects. A recent study simulated balance and compared the results with human data to distinguish the roles of biomechanics and neural control. The current work aimed to further corroborate the analysis by applying it to experimental data of humans balancing in challenging

conditions: in tandem stance and on a narrow beam. A method based on linear-quadratic programming was used to control a double-inverted pendulum model with torque-actuated ankle and hip joints corrupted with white noise. The controller parameters were designed to facilitate exploration of two important features: the relative cost between state deviation and control effort and the relative magnitude of hip and ankle effort. Simulation results were compared to 15 healthy subjects' force data to identify the best-fit parameter sets for a controller. In all balance conditions, the best-fit controller minimized the overall control effort. For some balance conditions, the best-fit controller's penalty on the ankle and hip joints varied in a physiologically-plausible manner. For example, when subjects stood on a narrow beam, the model that best fit the frontal plane data reduced the penalty in the hip compared to other conditions. This result aligns with the observation that the center of pressure, and thus the ankle torque, was constrained in the frontal plane due to the presence of the beam. These results suggest that human balance can be best described by a controller that maintains minimal control through the adjustment of relative ankle and hip joint torques. This work supports the applicability of the proposed method to identify the control strategies of quiet posture. This work was supported in part by NIH-R37-HD087089 and NSF-M3X-1825942 awarded to DS and in part by the Newman Fund. KS was supported by the Hugh Hampton Young Memorial Fund Fellowship.

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Poster

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Program #/Poster #: PSTR281.15/HH9

Topic: E.06. Posture and Gait

Title: Beta-gamma Phase Amplitude Coupling of Scalp Electroencephalography Can Predict Gait Disturbance in Parkinson's Disease.

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Osaka Univ., Suita City/ Osaka, Japan

Abstract: Background. There are many attempts to find biomarkers for the motor symptoms of Parkinson's disease. Adaptive deep brain stimulation system modulates stimulation using the beta-band power spectral density (PSD) from the subthalamic nucleus as an indicator to treat akinesia and rigidity in Parkinson's disease. However, it has difficulty improving postural reflex or gait disturbance by modulating stimulation. Recently, instead of PSD, beta-gamma phase amplitude coupling (PAC), which calculates the correlation of coupling between beta-band phase and gamma-band amplitude, has been increasingly reported to be an indicator of Parkinson's

disease symptoms. It is suggested that beta-band PSD in the basal ganglia reflects the signals relating motor symptoms whereas PAC is thought to represent the basal ganglia-cortical and cortico-cortical networks. Cortical PAC, not cortical PSD correlates with motor symptoms of Parkinson's disease. In this study, we evaluated whether PAC in scalp electroencephalography (EEG) can be a biomarker for gait disturbance. Methods. Cortical activities during 20m walking were measured using wireless scalp EEG in 11 patients with Parkinson's disease. Modulation index (MI) of beta-gamma PAC before and during walking was calculated from the signals on C3 and C4 in the 10-second sliding windows with 0.2 second step size. The MDS-UPDRS was evaluated before the trials, and the Postural instability and gait difficulty (PIGD) score was calculated as a subitem of UPDRS, which indicates freezing of gait (FOG) and gait instability. Results. Of the 28 trials, 20 trials had FOG score of 0 and 8 trials had FOG score of 1 or higher. Without FOG (0 point), MI was decreased significantly at the start of gait (p value=0.000714; MI at 10 seconds before walking=median: 0.71, 0.25-0.75 range: [0.31-1.74]; MI at the start of walking=0.46 [-0.09-0.99]), but with FOG (more than 1 point), MI did not decrease at the start of gait (p value=0.597; MI at 10 seconds before walking=0.86[0.66-1.23]; MI at the start of walking=0.81[0.36-1.33]). In addition, MI increased during walking in trials with higher PIGD scores, and MI and PIGD scores were positively correlated at 20 seconds after the start of walking (correlation coefficient=0.532, p value=0.000408). Conclusion. We found that the cortical PAC from scalp EEG reflects gait disturbance in subjects with PD. It is suggested that cortical network failure as well as basal ganglia deficits may be responsible for the gait disturbance or FOG in Parkinson's disease. This finding may provide important insights into the pathophysiology of gait disturbance in Parkinson's disease.

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Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.01/HH10

Topic: E.08. Respiratory Regulation

Support: R01-HL151389
R01-HL144801
R01-HL126523
P01-HL090554

Title: Chronically implanted Neuropixels identify distinct prefrontal cortex neural states during fentanyl-induced respiratory depression

Authors: ***Z. T. GLOVAK**[1], N. E. BUSH[1], G. LEÓN[1], M. M. MCKINNEY[1,2], J.-M. RAMIREZ[1,2,3];

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Abstract: Breathing during wakefulness is highly dynamic and varies as a function of an animal's behavioral state. Fentanyl causes significant respiratory depression and reduces electroencephalographic measures of arousal in rats (*Sci Rep* 9: 14122, 2019) and mice (*J Neurophysiol* 126: 1265, 2021). Reduced cortical arousal has been associated with decreased breathing (*Curr Biol* 28: 2145, 2018). The medial prefrontal cortex (mPFC) alters breathing (*Respir Physiol Neurobiol* 303: 103924, 2022) and behavioral arousal, however, the extent to which the mPFC modulates the relationship between arousal and breathing is not yet understood (*Trends Neurosci* 45: 722, 2022). This study is testing the hypothesis that systemic fentanyl administration induces a distinct neural state in the mPFC that correlates with changes in breathing. All methods adhered to the ARRIVE guidelines and were approved by the SCRI Institutional Animal Care and Use Committee. An adult male C57BL/6J mouse (n = 1, age = 20 wks) was anesthetized and implanted with a Neuropixel high-density probe aimed at the mPFC (1.94 mm anterior to bregma, 0.3 mm right of the midline). The probe was secured to the skull using a custom 3D printed headcap adapted from a previously validated model (*eLife* 8: e47188, 2019). After one week of recovery, the mouse was acclimated to a custom whole-body plethysmography chamber allowing for simultaneous measurement of mPFC local field potentials, single unit activity (n = 286), and breathing. Single unit Neuropixel recordings were viable for over 3 months. mPFC single neuron activity, as well as network activity quantified by principal components analysis, correlated with respiratory rate. Next, we subcutaneously administered fentanyl (0.1 mg/kg) which induced a depressed network state in the mPFC that also correlated with changes in breathing behavior. Compared to baseline, fentanyl significantly decreased population spiking activity in the mPFC ($p<0.01$, Wilcoxon rank-sum test) and caused a 50.1% decrease in respiratory frequency. These preliminary results are consistent with data from rats (*Sci Rep* 9: 14122, 2019) and indicate that decreased mPFC neuronal activity may contribute to fentanyl-induced respiratory depression. Ongoing studies are increasing sample size and exploring the feasibility of increasing cortex-driven arousal as a mitigation strategy for fentanyl-induced respiratory depression (*FASEB* 36: 00R71, 2022).

Disclosures: Z.T. Glovak: None. **N.E. Bush:** None. **G. León:** None. **M.M. McKinney:** None. **J. Ramirez:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.02/HH11

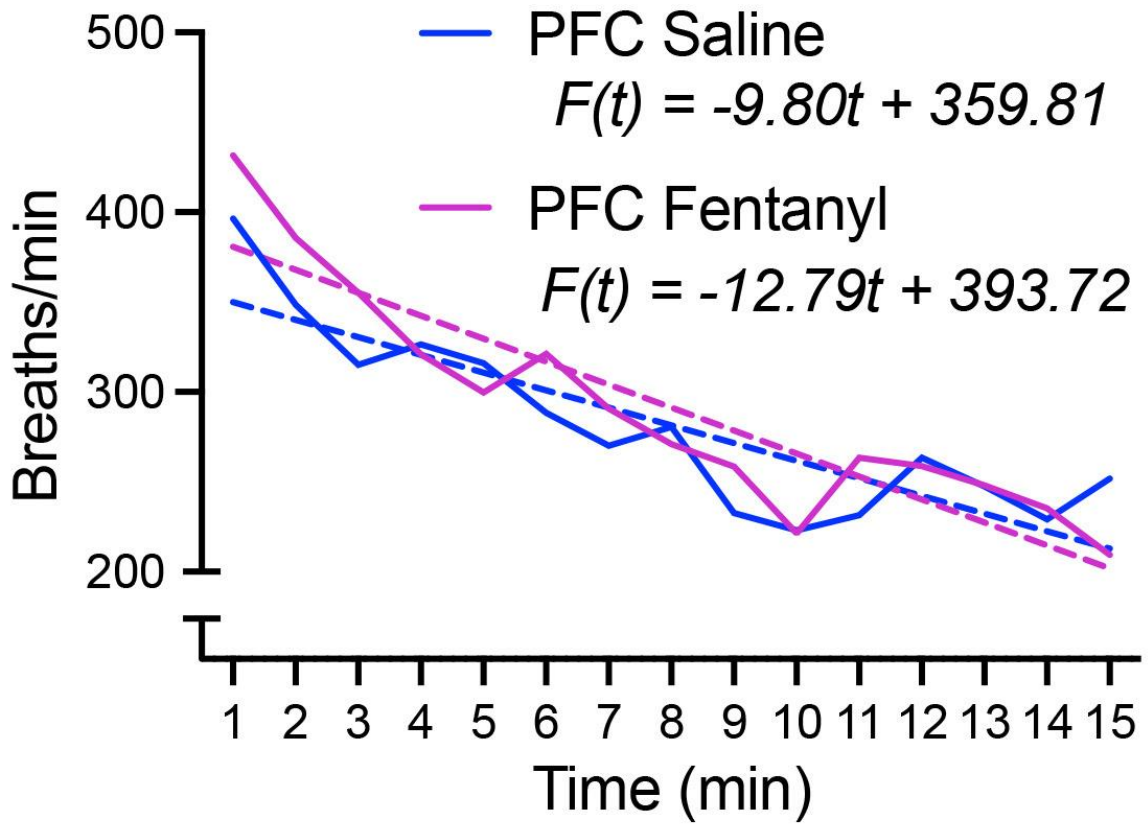
Topic: E.08. Respiratory Regulation

Support: Univ. Tennessee

Title: Decrease in respiratory rate caused by prefrontal cortex administration of fentanyl can be described using a gain modulation model

Authors: R. S. HERZOG[1], D. P. WOODS[2], Q. W. SUN[1], Z. T. GLOVAK[1], H. A. BAGHDOYAN[1], *R. LYDIC[1];
[1]Psychology, [2]Biomed. Engin., Univ. of Tennessee, Knoxville, TN

Abstract: Breathing rate of C57BL/6J (B6) mice is significantly increased by prefrontal cortex (PFC) microinjection of neostigmine (10.1016/j.resp.2022.103924). Gain modulation was recently used to describe one mechanism by which PFC neostigmine enhances breathing (https://jpet.aspetjournals.org/content/385/S3/139). The **objective** of the present study was to determine whether the decrease in breathing rate caused by PFC fentanyl microinjection also was consistent with the gain modulation model. All **methods** using mice were reviewed and approved by The University of Tennessee IACUC. Breathing measures were obtained from awake, male B6 mice (n=7) via DSI whole body plethysmography after PFC microinjection (50 nL) of saline (control) or fentanyl (1 nmol). In the following gain modulation model, $F_o = (1 + F_{tonic}k)\ F_i$, the terms F_i represent pre- and F_o post-fentanyl respiratory frequency, F_{tonic} represents baseline respiratory frequency, and (k) is a unitless, multiplicative modulation coefficient (10.1016/s1569-9048(02)00042-3). **Results** Breathing rate was plotted as a function of time after PFC administration of saline or fentanyl. Breaths per min were measured during min 1 through 15 after PFC microinjection. Trendline slopes (dashed lines) quantified respiratory rate modulation after PFC saline (-9.80) or PFC fentanyl (-12.79) administration. When expressed as a relative percent change, the modulation values reveal a 30.5% decrease in respiratory rate caused by PFC fentanyl, relative to PFC saline. **Conclusion** The present finding that PFC fentanyl injection caused a 30.5% decrease in breathing frequency contrasts with the previous finding that PFC neostigmine injection caused a 32.6% increase in breathing frequency. The bidirectional, time-dependent changes in breathing rate caused by PFC neostigmine versus PFC fentanyl support the hypothesis that the PFC alters breathing via gain modulation of brainstem respiratory rhythm generation.



Disclosures: **R.S. Herzog:** None. **D.P. Woods:** None. **Q.W. Sun:** None. **Z.T. Glovak:** None. **H.A. Baghdoyan:** None. **R. Lydic:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.03/HH12

Topic: E.08. Respiratory Regulation

Support: HL090554
HL126523
HL144801
HL151389
HL154558
R00HL145004
HL166317

Title: A Comparative Examination of Morphine and Fentanyl: Unraveling the Differential Impacts on Breathing and Airway Stability

Authors: *N. BURGRAFF[1], N. BAERTSCH[1,2], J.-M. RAMIREZ[1,2];
[1]Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA; [2]Univ. of Washington, Seattle, WA

Abstract: The global opioid crisis continues to highlight the urgent need for a comprehensive understanding of the wide-ranging impacts of various opioid substances. Among the consequences of opioid use, opioid-induced respiratory depression (OIRD) remains the most significant and is the primary cause of fatality from opioid overdose. This study provides an in-depth analysis of the distinct consequences of the opioid drugs morphine and fentanyl during OIRD. We explored the physiological implications of both drugs on ventilation and airway patency. Our results revealed a similar reduction in respiratory frequency with equivalent scaled dosages of fentanyl and morphine, though the onset of suppression was more rapid with fentanyl. Additionally, fentanyl resulted in transient airflow obstructions during the inspiratory cycle, which were absent following morphine administration. Notably, these fentanyl-specific obstructions were eliminated with tracheostomy, implicating the upper airways as a major factor contributing to fentanyl-induced respiratory depression. Additionally, vagotomy prevented the occurrence of airway obstructions, demonstrating the potential for increased central parasympathetic drive in causing the obstruction. We further demonstrate that bronchodilators salbutamol and epinephrine effectively reversed these obstructions, highlighting the bronchi's contribution to fentanyl-induced airflow obstruction. Our study also uncovered a significant reduction in sighs during OIRD, which were eliminated by fentanyl and markedly reduced by morphine. Finally, we found that fentanyl-exposed mice had reduced survival under hypoxic conditions compared to mice given morphine, demonstrating that fentanyl becomes more lethal in the context of hypoxemia. Our findings shed light on the distinct and profound impacts of these opioids on respiration and airway stability and lay the foundation for improved opioid use guidelines and more effective OIRD prevention strategies.

Disclosures: **N. Burgraff:** None. **N. Baertsch:** None. **J. Ramirez:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.04/HH13

Topic: E.08. Respiratory Regulation

Support: Fritz-Thyssen-Stiftung grant 10.20.1.004MN
DFG grant 450241946

Title: Identification of medullary neurons underlying congenital central hypoventilation syndrome

Authors: *K. CUI[1], Y. XIA[2], A. PATNAIK[3], L. HERNANDEZ-MIRANDA[4];
[1]Charité - Universitätsmedizin Berlin, Berlin, Germany; [2]Inst. für Zell- und Neurobiologie Charite Universitätsmedizin Berlin, berlin, Germany; [3]Charite Universtätsmedizin Berlin, berlin, Germany; [4]Charite Uviversitätsmedizin Berlin, Berlin, Germany

Abstract: Congenital Central Hypoventilation Syndrome (CCHS) is life-threatening respiratory disorder that is commonly dignosed in the childhood. The specific neural populations and circuits involved in CCHS pathogenesis are poorly understood. Here, we show that dysfunction of medullary neurons co-expressing Lbx1 and Phox2b (dB2 neurons) underlie CCHS. Using intersectional chemogenetics to transiently and reversely activate or silence dB2 neural activity, we show that these neurons play a crucial role in respiratory tidal volume dynamics, neonatal respiratory stability and the hypercarbic reflex, the natural acceleration of breathing in response to abnormally high levels of arterial pCO_2. dB2 neurons develop from rhombomere 2 to 6. To assess whether all or specific dB2 neuron subgroups (that is, dB2 neurons generated in distinct rhombomeres) regulate breathing homeostasis, we used distinct Cre-driver lines to diffentially ablate subgroups of dB2 neurons in a rhombomeric specific manner. We found that a specific subgroup of dB2 neurons (generated from rhombomere 5) is crucial for regulating the hypercarbic reflex. In addition, we also show that other dB2 neurons subgroups (generated from rhombomere 6) are essential for regulating respiratory tidal volumes and maintaining neonatal respiratory stability, and neonatal survival. Our study thus provides significant insights into the functional significance of dB2 neurons in respiration and in CCHS pathogenesis. Our data thereby add new neuroal components to the central respiratory circuit regulating breathing homeostasis, and provides with crucial knowledge that contributes to a deeper understanding of CCHS and its underlying pathophysiology.

Disclosures: K. Cui: None. **Y. Xia:** None. **A. patnaik:** None. **L. Hernandez-Miranda:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

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Program #/Poster #: PSTR282.05/HH14

Topic: E.08. Respiratory Regulation

Support: NIH F31 NS120467
R01HL137094
R01HL104101

Title: Glycinergic neurons contribute to features of Dravet syndrome

Authors: *B. M. MILLA[1], D. K. MULKEY[2];
[2]Physiol. & Neurobio., [1]Univ. of Connecticut, Storrs, CT

Abstract: Dravet syndrome (DS) is a severe form of epilepsy with a high incidence of sudden unexpected death in epilepsy (SUDEP.) Respiratory failure is a leading cause of SUDEP, despite

this it is unclear how DS-associated genetic variants or seizure activity disrupts respiratory control. Most DS cases are caused by mutations in the Scn1a gene encoding Nav1.1 channels preferentially regulating inhibitory neurons. Previously we showed that expression of a *Scn1a* loss of function variant (A1783V) in all inhibitory neurons resulted in seizures, breathing problems and premature death. However, it is unclear how loss of Scn1a function disrupts brainstem respiratory centers. To address this, we conditionally expressed $Scn1a^{A1783V}$ in subcortical brainstem respiratory centers by crossing floxed stop $Scn1a^{A1783V}$ mice with GlyT2-cre mice to generate GlyT2::$Scn1a^{A1783V/+}$ and control animals.
The novel open field assay was used to assess locomotor behavior and anxiety, EEGs characterized spontaneous and heat induced seizures, and whole-body plethysmography was used to assess baseline breathing and the ventilatory response to 3, 5 and 7% CO_2 (balance O_2). All experiments were performed in mice two months of age.
GlyT2::$Scn1a^{A1783V/+}$ mice were obtained at the expected frequency with grossly normal motor and anxiety behavior. These mice did not exhibit spontaneous seizures; however, 11 of 17 (~70%) GlyT2::$Scn1a^{A1783V/+}$ mice exhibited febrile seizures (at 42 ± .3 ºC.) Conversely, control mice do not show seizure activity over this same temperature range (n=12). GlyT2::$Scn1a^{A1783V/+}$ mice also showed reduced respiratory frequency (n=10) and increased post-sigh apnea (frequency and duration; n=7) under room air conditions and they showed a blunted ventilatory response to CO_2 compared to control mice.
Together, these results show that loss of Scn1a function in glycinergic neurons disrupts breathing and may increase febrile seizure propensity. Also, since febrile seizures are caused by respiratory alkalosis, these results suggest baseline breathing problems may serve as an early biomarker of febrile seizure propensity and risk of mortality in DS. These results show for the first time that disruption of glycinergic signaling contributes to clinically important aspects of DS.

Disclosures: B.M. Milla: None. **D.K. Mulkey:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.06/HH16

Topic: E.08. Respiratory Regulation

Support: JSPS KAKENHI Grant Number 20K07266

Title: Activation of Phox2b neurons in the dorsal brainstem induced sucking-like, swallowing-like and hiccup-like movements

Authors: *M. IIZUKA[1], K. IKEDA[2], H. IGARASHI[3], K. KOBAYASHI[4], H. ONIMARU[1], M. IZUMIZAKI[1];
[1]Dept. of Physiol., Showa Univ. Sch. of Med., Shinagawa-Ku, Japan; [2]Dept. of Oral Physiol., Showa Univ., Tokyo, Japan; [3]Robarts Res. Inst., Robarts Res. Inst., London, ON, Canada; [4]Fukushima Med. Univ., Fukushima Med. Univ., Fukushima 960-1295, Japan

Abstract: We found that photo stimulation of the dorsal skull of transgenic neonatal rats in which Phox2b positive neurons expressed one of the channelrhodopsin variants, ChRFR (C167A), caused rhythmic opening/closing movements of the mouth under conscious free-moving conditions. To examine detailed motor pattern, we recorded electromyograms from digastric, masseter and diaphragm muscles while video was recorded. During this rhythmic mouth movement, digastric muscle actives during the opening phase, and masseter muscle actives during the closing phase, suggesting the sucking activity. However, the extent of activation was dependent on the rats or trials, and there was digastric activity dominant pattern and masseter activity dominant pattern. The respiratory activities in the diaphragm were not correlate with the rhythmic activity in the digastric and masseter muscles. We also found other two types of rhythmic motor activity without apparent mouth movement. One was repetitive swallowing-like activity and another was hiccup-like activity. The swallowing-like activity was composed of the burst activity of the digastric muscle and the preceding the burst activity of diaphragm. Since the mouth did not open during the digastric muscle activity, it was thought that the hyoid bone was elevated and swallowing occurred at this time. To characterize hiccup-like activity, movement analysis was applied to not only mouth but also thorax and abdomen. The thorax and abdomen showed expanding movement during normal breathing. During hiccup-like movement, however, the thorax was dented in phase with the burst activity in diaphragm. This indicates the upper air way closed during the diaphragmatic activity. These results suggest that the activation of the Phox2b positive neurons in the dorsal brainstem is involved in triggering the sucking, swallowing and hiccup movement.

Disclosures: **M. Iizuka:** None. **K. Ikeda:** None. **H. Igarashi:** None. **K. Kobayashi:** None. **H. Onimaru:** None. **M. Izumizaki:** None.

Poster

PSTR282. Respiratory Rhythms

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Program #/Poster #: PSTR282.07/HH17

Topic: E.08. Respiratory Regulation

Support: NIH R01-AT010816
NIH R01-NS107296

Title: The role of intracellular calcium dynamics in sigh rhythmogenesis

Authors: *J. GU, M. STETTLER, D. BORRUS, C. GROVER, G. CONRADI SMITH, C. DEL NEGRO;
Col. of William and Mary, Williamsburg, VA

Abstract: The preBötzinger Complex (preBötC) of the lower brainstem generates inspiratory breathing rhythm giving rise to two distinct types of breaths: eupnea and sigh. Eupnea refers to normal breaths that ventilate the lungs whereas sigh breaths are characteristically greater in

volume and lower in frequency and are responsible for optimizing pulmonary function. However, the sigh-generating mechanism in the preBötC remains elusive. Here, we test a mathematical model of preBötC eupnea-sigh rhythmogenesis, wherein eupnea results from an excitatory network oscillator and sigh rhythm results from intracellular calcium dynamics in preBötC neurons. SERCA pumps and IP3 receptors modulate calcium uptake and release, respectively, in the endoplasmic reticulum. Nerve (CN XII) and field recordings were made from rhythmically active brainstem preparations that contain the preBötC in neonatal wildtype mice. We applied drugs that selectively block IP3 receptors and SERCA pumps. In line with model predictions, selective antagonism of IP3 receptors slows down or stops the sigh rhythm, and antagonism of SERCA pumps speeds up or stops sigh rhythm depending on drug concentration. By validating model predictions, we provide evidence that sighs are attributable to periodic calcium release from the endoplasmic reticulum and this rhythm operates independently with eupnea rhythm in the same cell population. This work advances our understanding of the neural basis of breathing and particularly the origin of sigh breaths, which are critical for the healthy functioning of compliant lungs in mammals.

Disclosures: **J. Gu:** None. **M. Stettler:** None. **D. Borrus:** None. **C. Grover:** None. **G. Conradi Smith:** None. **C. Del Negro:** None.

Poster

PSTR282. Respiratory Rhythms

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.08/HH18

Topic: E.08. Respiratory Regulation

Support: IRP of NINDS

Title: On the mechanisms of respiratory sensitivity to CO2: systematic review and meta-analysis of experimental and clinical evidence

Authors: N. PANZO[1], C. BRAGG[1], A. V. GOURINE[2], ***S. SHEIKHBAHAEI**[1];
[1]Neuron-Glia Signaling and Circuits, Natl. Inst. of neurological Disorders and Stroke, Bethesda, MD; [2]Neuroscience, Physiol. and Pharmacol., Univ. Col. London, London, United Kingdom

Abstract: Respiratory carbon dioxide (CO2) chemosensitivity is a crucial mechanism that regulates breathing in accordance with blood and brain PCO2/pH. Current models of central respiratory CO2 chemosensitivity focus on specialized neurons in the retrotrapezoid nucleus (RTN) and medullary raphé and suggest that these pools of neurons are primarily responsible for mediating the effects of CO2 on breathing. However, evidence also indicates the presence of CO2/pH-sensitive neurons in other brainstem areas. Further evidence suggests that astrocytes, non-neuronal cells, may also contribute to central CO2 chemosensitivity. All these data present key challenges in understanding regional specificity and the underlying mechanisms of respiratory CO2 chemosensitivity. We conducted a systematic review and meta-analysis of the

published primary literature to examine the relative contributions of different CNS sites and peripheral arterial chemoreceptors in mediating respiratory sensitivity to CO2 and the signaling mechanisms involved. The results of our analysis support the distributed central chemosensitivity hypothesis and indicate that central respiratory sensitivity to CO2 is mediated by multiple central chemoreceptor sites and the carotid body, with each region providing tonic drive to breathe in eucapnia and a fraction of the total response to systemic hypercapnia.

Disclosures: **N. Panzo:** None. **C. Bragg:** None. **A.V. Gourine:** None. **S. SheikhBahaei:** None.

Poster

PSTR282. Respiratory Rhythms

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Program #/Poster #: PSTR282.09/HH19

Topic: E.08. Respiratory Regulation

Support: HL090554
HL126523
HL144801
HL151389

Title: The impact of chronic intermittent hypoxia (CIH) on cellular/molecular functions of distinct cell types in the pons and medulla of adult mice as revealed by single-nucleus RNA sequencing.

Authors: *H. BHAGAVAN[1], A. D. WEI[1], J. M. RAMIREZ[1,2];
[1]Ctr. for Integrative Brain Res., Seattle childrens research institute, Seattle, WA; [2]Univ. of Washington, Seattle, WA

Abstract: Chronic intermittent hypoxia (CIH) is a prevalent condition that arises from recurring episodes of oxygen deprivation in respiratory disorders such as obstructive sleep apnea (OSA) and apneas of prematurity. Prolonged CIH impacts neuronal function, and leads to chronic inflammation, oxidative stress, and endothelial dysfunction, which are key factors in comorbidities including hypertension, metabolic disorders, and cardiovascular disease. Our objective is to understand the CIH-induced changes in gene expression (transcriptome) within different cell types of the brainstem. We performed a comparative analysis of the CIH response, leveraging highly multiplexed single-nucleus RNA sequencing (snRNA-seq). This enabled us to examine the expression profiles of 12,990 nuclei from six samples (C57BL6/J) of pontine-medullary adult tissues. Our analysis revealed the presence of major clusters, including neurons (9061), oligodendrocytes (3371), microglia (201), and astrocytes (357). Within the neuronal nuclei, we further identified 21 distinct subclusters broadly categorized as inhibitory (Gad1, Gad2, Slc32a1, and Slc6a5) and excitatory (vGlut1 and vGlut2) cell types. We uncovered dysregulated genes with a notable impact observed in inhibitory neurons and oligodendrocytes, while the dysregulation in excitatory cells was minimal (DESeq2; FDR corrected using

Benjamini-Hochberg, p-0.05). Pathway enrichment analysis revealed dysregulation associated with intrinsic membrane excitability (ion channels), synaptic transmission (neurotransmitter receptors), immune response, and structural remodeling (extracellular matrix and cell adhesion molecules) within the neuronal clusters. Oligodendrocytes exhibited dysregulation to oxidative stress. These observations contribute to our understanding of the molecular mechanisms underlying the impact of CIH in specific cell types and provide valuable insights for further investigation and potential therapeutic strategies.

Disclosures: H. Bhagavan: None. **A.D. Wei:** None. **J.M. Ramirez:** None.

Poster

PSTR282. Respiratory Rhythms

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Program #/Poster #: PSTR282.10/HH20

Topic: E.08. Respiratory Regulation

Support: NIH/NINDS R01 NS123155

Title: Comparison of intrinsic chemosensitivity of acutely dissociated medullary serotonergic neurons and retrotrapezoid neurons

Authors: Y. WU, E. BRAVO, ***G. RICHERSON**;
Univ. of Iowa, Iowa City, IA

Abstract: Rationale: Serotonergic neurons of the medullary raphe and Phox2b/Neuromedin B (Nmb) expressing neurons of the retrotrapezoid nucleus (RTN) are both putative respiratory chemoreceptors proposed to detect changes in CO_2/pH. However, their relative contribution to respiratory chemoreception is unknown. We directly compared their responses to hypercapnic and isocapnic acidosis after acute dissociation to study their intrinsic chemosensitivity.
Methods: The midline medulla was dissected from P10-P18 mice expressing YFP under control of the enhancer region of Pet1, which is selective for serotonergic neurons. Tissue was enzymatically digested and triturated, and plated onto glass coverslips etched with a grid for later identification of recorded neurons. Cells were fed with culture medium and allowed to attach to the substrate for 2-3 hours. Patch clamp recordings were then made in current clamp mode either immediately or after 1-8 days. In some cases, glial growth was inhibited by cytosine arabinoside. After recordings, coverslips were fixed with 4% formalin and immunostained with antibodies for MAP2 or GFAP, and it was determined whether any synaptic or glial contacts were present on recorded neurons. The same methods were used for RTN neurons except that dissections were made from P6-P11 Phox2b-Cre::Floxed tdTomato::ChAT-GFP mice, and recordings were made from Phox2b+/ChAT- neurons 1-2 days later. In some cases, neurons were stained for Nmb using RNAScope.
Results: In response to an increase in CO_2 from 5% to 9% (pH 7.4 to 7.2), 47 of 69 5-HT neurons (68%) increased their firing rate by more than 20% from baseline, with an average

response of 121%. In contrast, 11 of 32 RTN neurons (34%) increased their firing rate by more than 20% from baseline, with an average response of 37%. In response to isocapnic acidosis (pH 8 to 7), 43 of 61 5-HT neurons (70%) increased their firing rate by more than 50% from baseline, with an average response of 417%. In contrast, 9 of 64 RTN neurons (14%) increased their firing rate by more than 50% from baseline, with an average response of 122%. Preliminary data indicate that RTN neurons that were Nmb+ were not more likely to be chemosensitive, and 5-HT neuron responses were not larger if there were nearby processes or glia. There was no effect in either type of neuron of the number of days after dissociation.
Conclusions: Serotonergic neurons have a high degree of intrinsic (cell-autonomous) chemosensitivity. A smaller number of RTN neurons are chemosensitive and they have smaller responses, consistent with a more important role of the RTN as a relay from other chemoreceptor sites than as pH sensors.

Disclosures: Y. Wu: None. **E. Bravo:** None. **G. Richerson:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.11/HH21

Topic: E.08. Respiratory Regulation

Support: NIH Grant 1F31HL167553

Title: Enhanced peripheral chemoreception contributes to disordered breathing in Rett syndrome.

Authors: *M. STRAIN;
Univ. of Connecticut, Storrs, CT

Abstract: Enhanced peripheral chemoreception contributes to disordered breathing in Rett syndrome. Monica L. Strain[1], Michelle L. Olsen[2], Daniel K. Mulkey[1]. [1]Dept. of Physiology and Neurobiology, Univ. Connecticut, Storrs, CT, [2] School of Neuroscience, Virginia Polytechnic Institute and State Univ., Blacksburg, VA.
Rett syndrome (RTT) is a severe neurodevelopmental disorder caused by mutations in the methyl-CpG-binding protein 2 gene (MECP2). Symptoms of RTT include autistic-like behavior, seizures, and respiratory problems that typically manifest during wakefulness as episodes of hyperventilation followed by hypoventilation and apnea. The basis of respiratory dysfunction in RTT is not known; however, periodic breathing in general is predicted to result from over-activation of central or peripheral chemoreceptors that regulate breathing in response to hypercapnia or hypoxia, respectively. Therefore, the goals of this study are to characterize baseline breathing in MeCP2-deficient mice during the dark/active and light/inactive states, and to determine the extent to which central or peripheral chemoreception contributes to periodic breathing in this mouse model. All experiments were performed in adult (P40) male MeCP2-

deficient mice (MeCP2-/y; JAX #003890) and litter mate controls (n=6-7/genotype). Whole-body plethysmography was used to measure baseline breathing and ventilatory responses to graded increases in CO_2 (0-7% CO_2, balance O_2) and hypoxia (10% O_2, balance N_2). Reminiscent of RTT patients, we found that MeCP2-/y mice display severe periodic breathing in air with the phenotype being more pronounced in the wake state. We also found that MeCP2-/y mice have a normal ventilatory response to CO_2 ($p= 0.7661$) but exhibited an augmented ventilatory response to hypoxia ($p<0.0001$), particularly during the dark/active state. Interestingly, periodic breathing in MeCP2-/y mice was eliminated when peripheral chemoreceptor drive was diminished in 100% O_2. These results are consistent with previous work showing that loss of MeCP2 from peripheral sensory neurons recapitulated features of RTT including unstable breathing. Together, the findings from this study suggest that enhanced peripheral chemoreceptor drive contributes to diurnal periodic breathing in a mouse model of RTT.

Disclosures: M. Strain: None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.12/HH22

Topic: E.08. Respiratory Regulation

Support: JSPS KAKENHI 22H05557
JSPS Fellows 23KJ0245

Title: Endogenous hydrogen sulfide in the medullary respiratory center stabilizes the frequency and power of respiration in a regionally distinct way.

Authors: *M. OKAZAKI[1,2], T. KOGANEZAWA[1,3];
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Abstract: Hydrogen sulfide (H_2S) is synthesized in the central nervous system and regulates the neural network. We have found that inhibiting the H_2S synthase in the brain disrupts respiration. However, it is still unclear where in the medullary respiratory center and how the endogenous H_2S works. In this study, we aimed to investigate the contribution of the H_2S synthesized at each compartment of the medullary respiratory center to respiratory pattern generation and its underlying mechanism. We observed the central respiratory outputs by recording the phrenic and vagus nerve activity in the *in situ* arterially perfused preparation of decerebrated male rats. To identify the functional role of H_2S synthesized at each compartment of the medullary respiratory center, the pre-Bötzinger complex (pre-BötC), the Bötzinger complex (BötC), or the rostral VRG (rVRG), an H_2S synthase inhibitor was locally injected into each compartment of the medullary

respiratory center and the effects on the respiratory pattern were evaluated. Moreover, to investigate whether H_2S regulates respiratory output via modulating the synaptic transmission, an antagonist of a glutamatergic receptor or the cocktail of GABAergic and glycinergic receptors was locally injected. We compared the changes in the respiratory outputs by inhibiting H_2S synthesis in the absence and presence of those antagonists. When the H_2S synthase inhibitor was injected into the pre-BötC or the BötC, the amplitude of the inspiratory burst decreased, and the respiratory frequency increased according to the shorter inspiration or expiration, respectively. These respiratory changes were abolished or attenuated in the presence of the antagonist of a glutamatergic receptor. On the other hand, when the H_2S synthase inhibitor was injected into the rVRG, while the amplitude of the inspiratory burst was attenuated as similar to that at the pre-BötC or the BötC, the respiratory frequency decreased, which was the opposite alteration by injecting the cocktail of GABAergic and glycinergic receptors at the rVRG. These results indicate that the H_2S synthesized in each compartment of the medullary respiratory center functions to sustain the respiratory frequency and the power of inspiration in a region-dependent manner. The underlying mechanism might be the modulation of the excitatory and inhibitory synaptic transmissions.

Disclosures: **M. Okazaki:** None. **T. Koganezawa:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.13/HH23

Topic: E.08. Respiratory Regulation

Support: NIH Grant NS097492

Title: The role of phenytoin in generating multi-rhythmic inspiratory patterns in the preBötzinger Complex

Authors: *B. THADARI[1], K. KAM[2];
[1]Neurosci., Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL; [2]Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Breathing is a fundamental behavior that sustains life in mammals. While its primary function is gas exchange, intermixed with regular breathing are other rhythmic inspiratory patterns, such as sighing and sniffing, each with a distinct function. Inspiratory rhythm is generated by the preBötzinger Complex (preBötC). While a slower sighing rhythm interspersed with eupnea can be elicited with a neuropeptide injection into preBötC, a mechanism to produce shifts to faster inspiratory rhythms, as observed in sniffing, has not been determined. Changing regulators of preBötC excitability such as extracellular $[K^+]$ ($[K^+]_{ext}$) or extracellular $[Ca^{2+}]$ ($[Ca^{2+}]_{ext}$) can modulate inspiratory frequency, but appear insufficient to generate intermixed rhythmic inspiratory patterns *in vitro.* Persistent sodium current (I_{NaP}) also regulates preBötC

excitability, but the effects of partial blockade have not been rigorously explored. We hypothesized that alterations in I_{NaP} might produce unique dynamic states in preBötC that include intermixed inspiratory rhythms. We used rhythmically active transverse medullary slices (550-650 μm) from neonatal mice containing preBötC. We recorded inspiratory-related XII activity in response to bath application of phenytoin, a blocker of I_{NaP}. We found that applying phenytoin in increasing concentrations (125→225→325 μM) in ACSF containing 9mM $[K^+]_{ext}$ and 1.5 mM $[Ca^{2+}]_{ext}$ slowed down rhythm in a dose-dependent manner and, at 325 μM, ultimately stopped rhythm. During wash-off of phenytoin, we observed fast "runs" of 2-5 bursts, which we called "inspiratory multiplets," interspersed with the slower burst rhythm. Multiplets were absent once the burst rhythm fully recovered. We suggest that the brief appearance of slow and fast rhythmic bursting in preBötC represents a transitory multi-rhythmic state. To stabilize this multi-rhythmic state, we bath applied phenytoin in decreasing concentrations (185→50→10 μM) to mimic the phenytoin wash-off and increased excitability by lowering $[Ca^{2+}]_{ext}$ to 0.8 mM. While a few multiplets were interspersed with the slower inspiratory rhythm in 185 μM, multiplet generation was more robust after phenytoin was decreased to 50 or 10 μM. Multiplets occurred in phase with the burst rhythm, and the interval following a multiplet was longer than the average interburst interval, suggesting that preBötC burst- and multiplet-generating mechanisms interact. We conclude that combining changes in I_{NaP} and Ca^{2+} are one mechanism to achieve multi-rhythmicity in breathing. These findings contribute to our understanding of mechanisms underlying generation and modulation of breathing rhythm.

Disclosures: B. Thadari: None. **K. Kam:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.14/HH24

Topic: E.08. Respiratory Regulation

Support: NHLBI R00HL145004 (Baertsch)

Title: The role of enkephalinergic neurons in respiratory rhythm modulation

Authors: *G. LOGINOV[1], J. W. ARTHURS[1], N. A. BAERTSCH[1,2];
[1]Seattle Children's Res. Inst., Seattle, WA; [2]Univ. of Washington, Seattle, WA

Abstract: Opioid-induced respiratory depression (OIRD) is the primary cause of death during opioid overdose, characterized by diminished respiratory frequency and regularity. Activation of mu-opioid receptors (MORs) within the ventral respiratory column (VRC) of the medulla is partly responsible for the decrease in breathing following exogenous opioid administration. However, the role of MORs and endogenous opioid signaling in normal respiratory rhythm generation remains largely unknown. We hypothesized that endogenous opioids are released in the VRC to stabilize the respiratory rhythm under certain conditions of high network excitability.

To test our hypothesis, we used a combination of optogenetic and pharmacological approaches targeting endogenous MORs ligands -- enkephalins. Contrary to our expectations, optogenetic activation of enkephalinergic neurons in the preBötzinger Complex, the inspiratory rhythm-generating region of the VRC, increased the frequency of inspiratory bursts in brainstem slices of neonatal mice. These excitatory effects persisted after the application of MOR antagonist Naloxone, suggesting a non-MOR mediated mechanism. Further, high fidelity and temporal coordination of evoked bursts with optical stimulation implicated glutamatergic transmission as the primary source of excitation. In urethane-anesthetized spontaneously breathing mice, optogenetic activation of enkephalin-expressing neurons revealed anatomically dependent effects on breathing along the VRC. Continuous optical stimulation of the rostral VRC resulted in a significant decrease in respiratory frequency compared to spontaneous activity. However, activation of enkephalinergic neurons in the mid-VRC transiently increased the respiratory frequency and significantly increased breath amplitude. These findings suggest that the coexpression of enkephalin with other excitatory or inhibitory neurotransmitters may vary along the rostrocaudal axis of the VRC, resulting in differential effects of enkephalinergic neurons on respiratory rhythm. Alternatively, the functionally opposing effects of rostral and caudal enkephalinergic neurons may result from differences in their projection targets within the network. Future work will test these possibilities by dissecting enkephalinergic VRC inputs and local circuitry. Intersectional AAV approaches will allow for anatomical and functional characterization of enkephalin coexpression with glutamate or GABA within the network. These studies will help elucidate the role of endogenous enkephalinergic signaling and establish potential therapeutic targets for preventing OIRD.

Disclosures: G. Loginov: None. **J.W. Arthurs:** None. **N.A. Baertsch:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.15/HH25

Topic: E.08. Respiratory Regulation

Support: Ontario Graduate Scholarship
Canadian Institute of Health Research Canadian Graduate Scholarship Doctoral
Canadian Institute of Health Research Project Grant
Canadian Institute of Health Research Early Career Investigator Award in Circulatory and Respiratory Health

Title: Inhibitory prebötzinger complex neurons regulate rhythmic breathing in vivo

Authors: *K. BAKER[1,2], C. SCARPELLINI[2], G. MONTANDON[1,2];
[1]Inst. of Med. Sci., Univ. of Toronto, Toronto, ON, Canada; [2]St. Michael's Hosp. Keenan Res. Ctr., Toronto, ON, Canada

Abstract: Breathing is an essential process that is controlled by the rhythmic activity of brainstem breathing centers to generate respiratory rhythms. The preBötzinger Complex (preBötC) is a brainstem nucleus critical to generating breathing and contains excitatory and inhibitory cells that coordinate inhalation and exhalation. Approximately half the neurons in the preBötC are inhibitory and express γ-aminobutyric acid (GABA) or glycine but how these cells control respiratory rhythms is unknown. Additionally, brainstem breathing centers are vulnerable to drugs like sedatives such as benzodiazepines, which target these inhibitory circuits and can cause respiratory depression. To understand how these drugs cause respiratory depression, it is critical to first determine how the inhibitory cells in the brainstem control breathing. We aim to identify the role of inhibitory preBötC cells in the control of breathing in vivo.
To study the function of inhibitory preBötC cells, we used optogenetics to selectively activate and inhibit inhibitory preBötC cells with temporal precision. We stereotaxically injected a cre-dependent adeno-associated virus expressing either the excitatory channelrhodopsin or the inhibitory archaerhodopsin in the preBötC of vesicular GABA transporter (*vGAT*)-cre mice. Following the virus injection, we measured diaphragm activity in anesthetized mice and respiratory activity using whole-body plethysmography in freely behaving mice, while stimulating *vGAT* cells with blue (470 nm) light and inhibiting *vGAT* cells with green (554 nm) light to determine the functional output of these cells.
We found that *vGAT* excitation depresses breathing depending on the phase of the respiratory cycle when the laser stimulation occurred. Photostimulation of *vGAT* cells increased the delay between inspirations, therefore extending expiration. However, photostimulation of vGAT cells had no effect on inspiratory duration or the diaphragm amplitude in both freely behaving and anesthetized mice. Additionally, photoinhibition of *vGAT* cells increased respiratory rate by triggering inspiration before its natural occurrence, therefore decreasing expiratory duration. These data suggest that the preBötC inhibitory neurons are important for the initiation of inspiration as activating and inhibiting these cells alters when inspiration occurred. Our study is the first study to show the role of these inhibitory preBötC neurons in freely-behaving rodents. Our study contributes to a better understanding of the basic neural inhibitory circuits in the medulla regulating inspiration in freely-behaving rodents.

Disclosures: **K. Baker:** None. **C. Scarpellini:** None. **G. Montandon:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.16/HH26

Topic: E.08. Respiratory Regulation

Support: NIH Grant NS097492

Title: Inhibitory subpopulations in preBötzinger Complex play distinct roles in modulating inspiratory rhythm and pattern

Authors: *K. KAM, Z. CHANG, J. SKACH;
Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL

Abstract: Inhibition shapes breathing, walking, chewing, and other rhythmic motor behaviors, but, in many cases, the role of inhibitory neurons embedded within the mammalian neural circuits controlling these behaviors has not been rigorously determined. At the core of the neural circuit controlling breathing is the preBötzinger Complex (preBötC), a nucleus in the ventrolateral medulla necessary for generation of inspiratory rhythm. In the preBötC, a recurrently connected network of glutamatergic Dbx1-derived ($Dbx1^+$) neurons generates rhythmic inspiratory drive. Functionally and anatomically intercalated among $Dbx1^+$ preBötC neurons are inhibitory neurons defined by the GABAergic markers GAD1/GAD2 ($GAD1^+$/$GAD2^+$) and/or the glycinergic marker GlyT2 ($GlyT2^+$). Proposed roles for these neurons include modulation of burst pattern, tonic regulation of excitability, maintenance or coordination of phasic firing, and rhythm generation, but their function continues to be debated. We hypothesized that unrecognized heterogeneity among inhibitory preBötC neurons might explain the myriad roles proposed for these neurons. We first characterized the spatial distribution of molecularly-defined inhibitory preBötC subpopulations in double reporter mice expressing either the red fluorescent protein tdTomato or EGFP in $GlyT2^+$, $GAD1^+$, or $GAD2^+$ neurons. We found that, in postnatal mice, the majority of inhibitory preBötC neurons expressed a combination of GlyT2 and GAD2 while a much smaller subpopulation also expressed GAD1. To determine the functional role of these subpopulations, we used holographic photostimulation, a patterned illumination technique with high spatiotemporal resolution, to specifically excite small groups of $GlyT2^+$ or $GAD1^+$ preBötC subpopulations in rhythmically active medullary slices from $Dbx1^{tdTomato}$;$GlyT2^{EGFP}$ and $Dbx1^{tdTomato}$;$GAD1^{EGFP}$ double reporter mice. Stimulation of 4 or 8 $GlyT2^+$ preBötC neurons during endogenous rhythmic activity prolonged the interburst interval in a phase-dependent manner and increased the latency to burst initiation when bursts were evoked by stimulation of $Dbx1^+$ neurons. In contrast, stimulation of 4 or 8 $GAD1^+$ preBötC neurons did not affect interburst interval or latency to burst initiation, but did prolong both endogenous and evoked burst duration when stimulation occurred during the burst. We conclude that the majority of inhibitory preBötC neurons express both GlyT2 and GAD2 and affect breathing rhythm by delaying burst initiation while a smaller $GAD1^+$ subpopulation affects inspiratory patterning by prolonging burst duration.

Disclosures: **K. Kam:** None. **Z. Chang:** None. **J. Skach:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.17/HH27

Topic: E.09. Motor Neurons and Muscle

Support: R01NS114510

Title: A novel respiratory interneuron population sustains breathing under hypercapnia

Authors: *M. LIN, P. PHILIPPIDOU;
Dept. of Neurosciences, Case Western Reserve Univ. Sch. of Med., Cleveland, OH

Abstract: The ability to rapidly and reversibly modulate breathing in response to environmental challenges is essential for daily life. Under conditions of increased air CO_2 (hypercapnia), mammals breathe deeper to eliminate carbon dioxide intake. Phrenic motor neurons (PMNs) control breathing by integrating signals from diverse inputs to initiate the contraction of the major inspiratory muscle, the diaphragm. While central chemoreceptors that can sense changes in carbon dioxide levels have been identified, it is unknown whether PMN activity can be regulated directly by first-order inputs to adapt to hypercapnic challenges. Here, we mapped first-order inputs to PMNs, and discovered a local spinal cholinergic interneuron population that contributes around 10% of total PMN inputs. These interneurons are located within cervical levels of the spinal cord and are highly activated under a hypercapnic challenge. In addition, specifically silencing cholinergic neurotransmission in these interneurons impairs the breathing response under moderate, but not mild, hypercapnia (10% CO_2) specifically in adult mice, indicating the function of spinal cholinergic modulation in breathing is age- and intensity-dependent. Our findings identify a novel respiratory population with the ability to respond to hypercapnia and implicate spinal first-order PMN inputs in regulating breathing.

Disclosures: M. Lin: None. **P. Philippidou:** None.

Poster

PSTR282. Respiratory Rhythms

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.18/HH28

Topic: E.08. Respiratory Regulation

Support: Tenovus Scotland Grant T20-09

Title: Modulation of Breathing by Spinal Cholinergic Pathways

Authors: *G. CALABRESE[1], M. J. BROADHEAD[1], K. A. SCHARDIEN[2], A. V. INCOGNITO[3], M. A. LANE[2], R. J. A. WILSON[3], S. A. SHARPLES[1], G. B. MILES[1];
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Abstract: Breathing must be readily adjusted to meet changing metabolic demands. It is well established that the rhythm is generated in the brainstem; however, mounting evidence points toward roles for cervical spinal interneurons (INs) in adjusting respiratory output.
Here we used a combination of mouse genetics, immunohistochemistry, calcium imaging and electrophysiology to study spinal cholinergic modulation of breathing and interrogate underlying

neural mechanisms. We focused on C-boutons - large cholinergic modulatory synapses derived from Pitx2$^+$ INs previously shown to facilitate motoneuron (MN) output in a task-dependent manner, via M2 muscarinic receptor signaling.
Anatomical studies utilized mice that express a red fluorescent protein in Pitx2$^+$ INs. Phrenic MNs were retrogradely labelled via either intrapleural injection of cholera toxin B subunit or by applying pseudorabies virus to the diaphragm. For functional analysis, respiratory activity was recorded *in-vitro* from the C3/4 ventral roots of isolated brainstem-spinal cord preparations from neonatal mice, or *in-situ* from the phrenic nerve in working heart-brainstem preparations from adult rats. Calcium dynamics were visualized *in-vitro* using tissue from mice expressing GCAMP6s in Pitx2$^+$ INs.
We found that Pitx2$^+$ INs form synapses onto phrenic MNs. We also found that cervical Pitx2$^+$ INs are active during respiration, albeit not in phase with individual bursts of respiratory motor output. Pharmacological blockade of M2 receptors reduced the amplitude and increased the frequency of respiratory-related activity *in-vitro*. The reduction in amplitude was reproduced when M2 receptors were selectively blocked in the cervical spinal cord, suggesting endogenous spinal cholinergic modulation through M2 receptors. *In-situ* experiments confirmed that M2 modulation of phrenic MN output is also present in the adult. However, modulating Pitx2$^+$ IN activity in animals expressing excitatory or inhibitory DREADDs did not alter respiratory-related output *in-vitro*, suggesting that these INs might not be involved in maintaining respiratory output at the early postnatal period. Interestingly, preliminary data suggests that hypercapnic facilitation of diaphragm activity may be diminished in animals where cholinergic Pitx2$^+$ INs are genetically ablated, implying a role in facilitating breathing during states of increased metabolic demand. Together, these data demonstrate a role for cholinergic modulation in the maintenance of respiratory output that is intrinsic to the cervical spinal cord and lasts throughout development, although the contribution of C-boutons to this modulation remains unclear.

Disclosures: G. Calabrese: None. **M.J. Broadhead:** None. **K.A. Schardien:** None. **A.V. Incognito:** None. **M.A. Lane:** None. **R.J.A. Wilson:** None. **S.A. Sharples:** None. **G.B. Miles:** None.

Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.01/II1

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Helene and Viggo Bruuns Fond

Title: Unravelling the role of the putative proton-coupled organic cation antiporter in triptan transport across the blood-brain barrier

Authors: *N. SVANE[1], A. PEDERSEN[1], A. RODENBERG[1], B. OZGÜR[1,2], L. SAABYE[1,3], M. KRISTENSEN[1], C. BUNDGAARD[2], P. TFELT-HANSEN[4], B. BRODIN[1];

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Abstract: Triptans are 5-hydroxytrytamine$_{1B/1D}$ receptor agonists used to treat migraines. The anti-migraine effect of triptans involves peripheral mechanisms that counteracts migraine-associated intracranial vasodilation. Besides peripheral mechanisms, there are indications suggesting that triptans may also act on $5HT_{1B/1D}$ receptors within the central nervous system, although the exact mechanism by which this occurs is not well understood (1). Triptans are believed to have limited ability to passively cross the blood-brain barrier (BBB) due to their relatively hydrophilic nature (1). This study aimed to assess the role of the putative proton-coupled organic cation (H^+/OC) antiporter in the uptake of triptans into brain capillary endothelial cells and to examine whether triptans interacted with the efflux transporter, P-glycoprotein (P-gp). We applied human brain capillary endothelial cells (hCMEC/D3) to investigate uptake characteristics of prototypical H^+/OC antiporter substrates and triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan). Time-, concentration-, and pH-dependent uptake was evaluated, as well as inhibitory properties. In addition, we applied porcine epithelial cells (IPEC-J2) transfected with human MDR1 to study P-gp-mediated efflux of triptans across IPEC-J2 MDR1 monolayers. We demonstrated functional expression of the H^+/OC antiporter in hCMEC/D3 cells. Prototypical substrates of the H^+/OC antiporter, [^{3}H]-pyrilamine and oxycodone, exhibited time-, concentration-, and pH-dependent uptake into hCMEC/D3 cells. The triptans revealed varying degrees of inhibition on the uptake of [^{3}H]-pyrilamine with IC50 values ranging from 15 ± 4 to 1729 ± 1209 µM. Among the triptans, eletriptan exhibited the strongest inhibitory effect, as well as time-, concentration-, and proton-dependent uptake into hCMEC/D3 cells. Furthermore, only eletriptan interacted with the P-gp efflux transporter demonstrating an efflux ratio of 28.9 ± 1.8, which was eliminated in the presence of the P-gp inhibitor, zosuquidar. In conclusion, we found that some triptans, particularly eletriptan, can be transported into the brain endothelium via the putative H^+/OC antiporter. This study provides valuable insights into the molecular mechanisms of triptan transport into and across the BBB, which may contribute to a deeper understanding of potential central mechanisms of triptans in migraine treatment.(1) Tfelt-Hansen PC. Does sumatriptan cross the blood-brain barrier in animals and man? J Headache Pain. 2010;11(1):5-12.

Disclosures: **N. Svane:** None. **A. Pedersen:** None. **A. Rodenberg:** None. **B. Ozgür:** None. **L. Saabye:** None. **M. Kristensen:** None. **C. Bundgaard:** None. **P. Tfelt-Hansen:** None. **B. Brodin:** None.

Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.02/II2

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: IM2PACT 807015

Title: Modeling the mouse blood-brain barrier: A simple method for generating mouse brain endothelial cell monolayers

Authors: *A. B. V. PEDERSEN[1], H. C. C. HELMS[2], B. OZGÜR[1], M. KRISTENSEN[1], B. BRODIN[1];
[1]Univ. of Copenhagen, Copenhagen, Denmark; [2]Danish Medicines Council, Copenhagen, Denmark

Abstract: The brain capillary endothelium forms the blood-brain barrier (BBB), tightly regulating drug transport into the brain. This poses a challenge for developing new central nervous system (CNS) drugs. *In vitro* BBB models using brain capillary endothelial cells (BECs) are valuable for drug screening, studying cell interactions, and predicting transport rates. However, translating results from non-rodent BBB models to preclinical rodent models is hindered by species-specific differences. Therefore, a validated mouse BBB model is needed to overcome these limitations. In this study, we aim to establish a validated monoculture *in vitro* BBB using primary BECs for transendothelial transport studies. To establish the model, the cortex from 4-week-old C57BL/6 male mice was harvested and homogenized. Brain capillary fragments were isolated through several steps, including centrifugation with dextran and enzyme treatment. After 9 days of cultivation, the isolated mouse BECs were prepared for experiments. Primary mouse BECs were used to develop monoculture models on Transwell supports. The successful formation of tight junctions was confirmed through immunocytochemical staining, which illustrated the location of junctional claudin-5 and ZO-1. The functional tightness was demonstrated by transendothelial electrical resistance (TEER) measurements and permeability studies using the small hydrophilic molecule, mannitol (180 Da). The identity of the isolated mouse BECs was validated through immunocytochemical staining and gene expression analysis of cell-specific proteins, including von Willebrand Factor (vWF), platelet derived growth factor receptor beta (Pdgfrβ) and platelet and endothelial cell adhesion molecule 1 (Pecam1). Notably, the presence of P-glycoprotein has been demonstrated in previously studies (Hinca et al., 2021). These results demonstrate that the established mouse BBB model using monocultured BECs successfully formed monolayers with functional tight junctions. The purity of the isolated cells as endothelial cells was confirmed. This validated mouse BBB model serves as a valuable tool for studying transendothelial transport experiments and holds promise for the development of accurate and translatable preclinical models in CNS drug discovery. Reference: Hinca SB, Salcedo C, Wagner A, Goldeman C, Sadat E, Aibar MMD, et al. Brain endothelial cells metabolize glutamate via glutamate dehydrogenase to replenish TCA-intermediates and produce ATP under hypoglycemic conditions. J. Neurochem. 2021;157(6):1861-1875.

Disclosures: A.B.V. Pedersen: None. **H.C.C. Helms:** None. **B. Ozgür:** None. **M. Kristensen:** None. **B. Brodin:** None.

Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.03/II3

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH/NCI 1R01CA245969-01A1
NIH/NCI 1U19CA264338-01

Title: Characterizing the acute endothelial response to ultrasound-based blood-brain barrier opening: a transcriptional and ultrastructural analysis

Authors: *A. GOULD[1,6], Y. LUAN[1,2], Y. HOU[1,2], F. V. KORBOVA[1,7], L. CHEN[1,6], C. AMIDEI[1,6], R. WARD[1,6], C. GOMEZ[1,6], M. KOBAYASHI[2], B. CASTRO[1,6], D. Y. ZHANG[1,6,8], M. YOUNGBLOOD[1,6], V. A. ARRIETA[1,6], K. HABASHY[1,6], H. NAJEM[1,6], K. KIM[1,6], R. SAGANTY[1,8], C. DMELLO[1,6], J. BEBAWY[1,3], G. BOUCHOUX[9], R. STUPP[1,6,4,5], M. CANNEY[9], F. YUE[2], L. I. ARISPE[7], A. M. SONABEND[1,6];
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Abstract: Temporary compromise of blood-brain barrier (BBB) integrity is commonly observed in acute neurological disease states. Endothelial cells are a key component of the BBB, and thus barrier dysfunction is associated with structural and molecular changes to these cells. Previously, we used low-intensity pulsed ultrasound with microbubbles (LIPU/MB) to enhance drug delivery to the brains of humans. This temporary and targeted model of BBB dysfunction offers an opportunity to study how these endothelial cells respond to loss of barrier integrity and potentially initiate repair. To do this, we used single-cell RNA sequencing (scRNAseq) and transmission electron microscopy (TEM) to examine transcriptional and structural changes in the cerebral endothelium after inducing targeted BBB dysfunction by LIPU/MB in patients (n = 6) undergoing surgical resection of recurrent glioblastoma. We used intraoperative fluorescent microscopy and fluorescein administered after LIPU/MB to identify and to biopsy “sonicated” brain tissues with evident BBB dysfunction, alongside “non-sonicated” control tissues. On a Uniform Manifold Approximation and Projection (UMAP) plot, sonicated and non-sonicated endothelial cells formed distinct clusters. The sonicated cells exhibited unique gene expression profiles, with alterations in various genes previously linked to BBB function such as *MFSD2A, Cav1, VE-Cadherin, COL4A1*,and specific SLC-family transporters. These changes aligned with gene ontology themes such as *Regulation of Endocytosis, Cell-Cell Adhesion, Cell-Matrix Adhesion, Cell Migration,* and *Abnormality of the Cerebral Vasculature.* Further, TEM analysis revealed a time-dependent shift in endothelial structure, with a decrease in the number of endothelial caveolae and an increase in cytoplasmic vacuoles. Sonicated capillaries demonstrated granular deposits within the basement membrane, and rarefaction of the cytosol.Our transcriptional data are likely reflective of the mechanical nature of LIPU/MB-mediated BBB dysfunction, where the endothelium is attempting to reestablish inter-cellular connections and to reattach to the basement membrane, while simultaneously addressing the ionic imbalances induced by transient BBB dysfunction. We also observed transcriptional and TEM evidence of diminished caveolar transcytosis shortly after LIPU/MB, which could reflect the secondary ability of caveolae to serve as membrane buffers that accommodate to mechanical stretching of

the cell membrane. Future studies should investigate these pathways as mechanisms of barrier repair for neuro-protective benefit in other models of BBB dysfunction.

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Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.04/II4

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH grant 2RF1AG039452-06
NIH grant AG023084
NIH grant NS034467

Title: Functional properties of human pluripotent stem cell-derived brain pericytes

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Abstract: Brain vascular dysfunction contributes to the development of neurodegenerative disorders, including Alzheimer's disease (AD). We and others have shown that pericytes, which are vascular mural cells embedded in the wall of brain microvessels, play an essential role in regulating blood-brain barrier (BBB) integrity, controlling cerebral blood flow, clearing neurotoxins, providing neurotrophic support, and angiogenesis. Previous studies by our group have shown that pericyte degeneration and loss occurs in AD and that pericyte loss in the AD mouse model results in a significant increase in BBB leakage and neuronal loss. The goal of the present investigation is to generate and characterize induced pluripotent stem cell (iPSC)-derived forebrain pericytes (iPSC-PCs), then to assess their potential as a cell therapy treatment. First, we show by quantitative proteomic analysis that iPSC-PCs share 96% of total proteins and 98% of protein phosphorylation sites with primary adult human brain pericytes. Then, we show that

iPSC-PCs home to microvessels in live brain tissue slices from pericyte-deficient mice. Finally, we show that transplantation of iPSC-PCs into hippocampi of pericyte-deficient mice leads to restoration of BBB integrity and improved neuronal retention. These fully-characterized iPSC-PCs that share molecular and phenotypic similarities with endogenous human adult brain microvascular pericytes hold potential as a future non-neuronal, pericyte-based cell therapy for AD and related neurodegenerative disorders.

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Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

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Program #/Poster #: PSTR283.05/II5

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R61HL159948 (MUG, BH, HK)
MCB Summer Undergraduate Research Fellowship (AN)
Beckman Institute Undergraduate Fellowship (AN)

Title: Circadian Dynamics of Blood-Brain Interface Endothelial Cells and Tight-Junction Proteins

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Abstract: Strokes and bleeding in brain parenchyma are cerebrovascular events that can cause long-term dysfunction. Stroke alone affects >795,000 people in the U.S. annually. The occurrences of strokes and microbleeds are not random; they occur in the early day and early night. Intracerebral bleeding will cause further havoc to brain homeostasis by increasing permeability of the blood-brain interface (BBI). Recent evidence suggests that components of the BBI are under circadian regulation, but the circadian dynamics of the BBI endothelial cells' circadian clocks and tight junction proteins are yet to be determined. In this report, we studied the daily variations of BBI endothelial cells isolated from mice bearing a clock fluorescent reporter, Per1-Venus. We found that after synchronization of BBI endothelial cells by dexamethasone, Per1-Venus expression over 24-h peaked at 8-h and 16-h post-synchronization ($p < 0.0001$, one-way ANOVA of mean fluorescent intensity (MFI)). The clock reporter expression in isolated brain microvessels showed a similar pattern of variation. The permeability of the BBI is determined by tight junctions between brain endothelial cells and, thus, may be

influenced by circadian rhythms. Hence, we also investigated a key tight-junction protein of rodent brain microvessels, Claudin-5. We examined temporal expression and localization of Claudin-5 over the day-night cycle. Based on western blot and immunofluorescent results, we found two significant peaks of Claudin-5 expression and localization over 24-h ($p < 0.001$, one-way ANOVA of MFI). We performed transepithelial/transendothelial electrical resistance (TEER) assays to measure barrier tightness between primary brain endothelial cells. The TEER assay is non-invasive and offers the advantage of continuously monitoring living cells throughout the circadian cycle. When we monitored the integrity and permeability of the *in vitro* barrier between endothelial cells for 4 days, we found that permeability fluctuated significantly according to time-of-day ($p < 0.001$, one-way ANOVA of TEER measurements). We found two daily peaks in permeability about 12-h apart. Our findings indicate that endothelial cells of the BBI possess self-sustained autonomous clocks, circadian-dependent expression of the tight junction protein, Claudin-5, and time-of-day-dependent variation in a functional measure of permeability. These results may address the periods of vulnerability to stroke and cerebral microbleeds in early morning and evening. Further research will contribute to the prevention, treatment, and long-term care for stroke patients based on circadian rhythms.

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Poster

PSTR283. Blood-Brain Barrier

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.06/II6

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01NS113912

Title: Role of extracellular vesicles in iron transport to the mice brain

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Abstract: Iron is essential for normal brain development and function. Hence, understanding the mechanisms of iron efflux at the blood-brain barrier and their regulation is critical for establishing brain iron homeostasis. Herein we investigated the role of extracellular vesicles (EVs) in mediating the transfer of Transferrin (Tf) bound iron to the mice's brains. EVs secretion is prevented by inhibition of neutral sphingomyelinase 2 (nSMase2), a key regulatory enzyme generating ceramide from sphingomyelin, with GW4869. Using the C57BL/6 mice, we show that intraperitoneal injection of GW4869 reduces the levels of brain and serum EVs compared to the control. When mice were injected intraperitoneally with ^{57}Fe-Tf, the ^{57}Fe concentration in the brain parenchyma was decreased compared to the control group. Furthermore, the EVs inhibition increased the retention of ^{57}F in the brain microvasculature compared to the control group

suggesting ^{57}Fe-Tf uptake into the microvasculature is not interrupted but release into the brain is negatively impacted. In addition, EVs synthesis inhibition decreased the serum iron levels, whereas the liver iron levels increased compared to the control group. These results indicate that blood-brain barrier endothelial cells release EVs and those EVs are mediating a major iron delivery pathway to the brain.

Disclosures: K. Palsa: None. **E. Neely:** None. **I.A. Simpson:** None. **J.R. Connor:** None.

Poster

PSTR283. Blood-Brain Barrier

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Program #/Poster #: PSTR283.07/II7

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: 5R21NS116431-02

Title: A mouse model of the CCM1/KRIT1 mutation causing human cerebral cavernous malformations

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Abstract: Cerebral cavernous malformations (CCM) are typically modeled in the mouse using conditional Cre/lox recombination systems, resulting in the deletion of a large portion of the causative gene after induction with tamoxifen. However, these genetic changes are not consistent with human neuropathology, which is usually due to single nucleotide polymorphisms (SNP), or small DNA rearrangements such as microdeletions. This discrepancy complicates experimental approaches to gene therapy in the mouse model. To provide a more translational genetic system, we injected fertilized mouse eggs with Cas9, sgRNA, and ss donor DNA to mutate codon # 455 in *Krit1*, which is one of the most common pathogenic mutations in the human *KRIT1* gene. To this end, we created a 13-bp microdeletion in exon 11 of *Krit1*. This mutation causes a premature polypeptide termination, which is very similar to the nonsense Gln455Ter *CCM1(KRIT1)* mutation originally discovered in the Mexican-American Hispanic population. Next, the identified founders harboring the mutation were bred to *Krit1* "floxed" animals and the *Cdh5-CreERT2* strain. The animals harboring *Cdh5-CreERT2; Krit1-flox/13del* animals were induced with tamoxifen on postnatal day P5 and the mice were characterized with MRI and histology. We found that the 13del allele is pathogenic and causes brain lesions. We have also found splenomegaly in these mice that appears to be related to enlarged blood vessels in splenic red pulp. This phenotype leads to early mortality at 1-2 months of age. Our new model of *Krit1* can facilitate future approaches to gene therapy for this vascular disease.

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Poster

PSTR283. Blood-Brain Barrier

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.08/II8

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: RCN

Title: Physiological roles of the choroid plexus: lessons learnt from the zebrafish

Authors: *N. JURISCH-YAKSI[1], I. JEONG[1], S. N. ANDREASSEN[2], M. POULAIN[4], M. FÜRTHAUER[4], H.-C. PARK[5], N. MACAULAY[3];
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Abstract: The choroid plexus produces cerebrospinal fluid (CSF) in the brain, by uptaking nutrients and water from blood vessels via various transporters. Disturbed fluid homeostasis by the choroid plexus is one of common causes of hydrocephalus. Accumulating evidence suggests that the choroid plexus plays additional roles in brain development and homeostasis by secreting neurotrophic molecules, serving as a CSF-blood barrier and an immune interface. Yet, how the choroid plexus impacts brain physiology remains understudied. To provide novel insights into the physiological roles of the choroid plexus, we use zebrafish juvenile and adult as model systems. We first identified upon histological and transcriptomic analyses that the zebrafish choroid plexus is highly conserved with the mammalian choroid plexus and that it expresses all transporters necessary for CSF secretion. Using a novel transgenic line, we also identified that the choroid plexus actively secretes proteins into the CSF. Next, we developed a genetic tool to ablate epithelial cells specifically in the choroid plexus. Using the ablation system, we identified a reduction of the ventricular volume but no leakage of tracers at the CSF-blood barrier. Altogether, we observed that the zebrafish choroid plexus is evolutionarily conserved and critical in maintaining CSF homeostasis, which sets the basis for our long-term goal to unravel how the choroid plexus modulates brain physiology in health and diseases.

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Poster

PSTR283. Blood-Brain Barrier

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.09/II9

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01 MH121763

Title: Ahnak function in cerebrovascular endothelial cells and behavioral adaptations to chronic stress

Authors: *Y. JEONG[1], B. CARABELLI[1], D. BHATTI[2], M. CHEN[3], J. DYKE[4], Y. KIM[1,5]; [1]Robert Wood Johnson Med. School, Rutgers Univ., Piscataway, NJ; [2]Harvard Univ., Cambridge, MA; [3]Carver Col. of Medicine, Univ. of Iowa, Iowa City, IA; [4]The Citigroup Biomed. Imaging Center, Weill Cornell Med. Col., New York, NY; [5]Brain Hlth. Institute, Rutgers Univ., Piscataway, NJ

Abstract: The blood-brain barrier (BBB) plays a vital role in the exchange of molecular substances between the blood and brain to maintain central nervous system (CNS) homeostasis and its proper function. The barrier property of the BBB is given by endothelial cells in the blood vessels in the brain. The tight control of the molecular transport via endothelial cells is necessary to supply nutrients and protect the brain from toxic substances, and the BBB dysfunctions underlie the pathophysiology of several neurological disorders and psychiatric disorders. Thus, it is important to identify key molecular factors and pathways mediating transport mechanisms in endothelial cells and investigate their alterations in brain disorders. We have found that Ahnak expressed in vascular endothelial cells (EVs) in the brain is a novel regulator of behavioral adaptations in response to chronic stress. In a mouse chronic social defeat stress (CSDS) paradigm, the protein levels of hippocampal Ahnak are lower in stress-resilient mice but higher in stress-susceptible mice compared to the levels in non-defeated mice, being inversely correlated with social interaction scores. Ahnak is highly expressed in ECs in the hippocampus. However, the function of Ahnak in vascular ECs is unknown. To investigate Ahnak function in ECs, we have generated EC-specific Ahnak KO mice. Interestingly, EC-specific Ahnak KO mice display baseline antidepressant-like behavior and stress-resilient phenotype in the CSDS paradigm. We have also observed that EC-specific Ahnak deletion does not cause BBB disruption, and Ahnak does not colocalize with tight junction proteins. Instead, Ahnak protein is mainly expressed in vesicles in ECs. Our EC-specific translational profiling data indicates alterations of several molecule transporters in Ahnak-deleted ECs. Our study suggests that antidepressant-like behavior or stress resilience can be induced by targeting Ahnak pathway in vascular endothelial cells in the brain.

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Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.10/II10

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Multiple exposures to the anesthetic sevoflurane cause blood vessel regression in the neonatal mouse hippocampus

Authors: *Y. MATSUMOTO, M. TORII;
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Abstract: Children who receive multiple exposures to anesthesia for surgery may have an increased risk of developing cognitive impairment. Sevoflurane, a commonly used anesthetic in clinical practice, has been reported to induce permeability of the adult blood-brain barrier (BBB), which is pivotal to maintain the homeostasis of brain microenvironment, leading to perioperative neurocognitive dysfunction. However, the effect of sevoflurane on blood vessels in the neonatal brain remains unclear. This study aims to reveal the impact of multiple exposures to sevoflurane on the vasculature of the hippocampus in neonatal mice. C57BL6/J mice in the anesthesia group received inhalation of sevoflurane (3%) plus 40% oxygen (balanced with nitrogen) for 2 hours daily for 3 consecutive days (P6 to P8). Mice in the control group received only 40% oxygen. Brain slices were collected on post-anesthesia day (PAD) 1, 7, 14, 21, and 28, and stained for the basement membrane and endothelial cells with anti-CollagenIV and anti-CD31 antibodies, respectively, to investigate structural changes in brain blood vessels after anesthesia. Some parts of CollagenIV+ blood vessels in the CA1 regions of the hippocampus lacked CD31 expression, as an indication of the blood vessel regression. The number of such CollagenIV+/CD31- blood vessels per field of view in the anesthesia group (mean ± SD: 5.33 ± 3.3, n=6) was higher than that in the control group (1.00 ± 0.63, n=6) on PAD7. This number on PAD7 was also higher than those on PAD1 (2.50 ± 1.4, n=6) and PAD28 (1.83 ± 1.7, n=6) in the anesthesia group. The CollagenIV+/CD31- blood vessels on PAD28 lacked cell nuclei assessed by 4’,6-diamidino-2-phenylindole (DAPI) staining, suggesting the loss of endothelial cells on those blood vessels. We also detected extravascular IgG around the CollagenIV+/CD31- blood vessels, indicating BBB breakdown. These results collectively suggest that multiple exposures to sevoflurane induce pathological regression of blood vessels in the neonatal hippocampus through its impacts on endothelial cells, causing the breakdown of BBB and disrupting the homeostasis of brain microenvironment. These findings would facilitate mechanistic studies on anesthesia-induced neurotoxicity in young patients.

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Poster

PSTR283. Blood-Brain Barrier

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Program #/Poster #: PSTR283.11/II11

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Applications of a human iPSC-derived blood-brain barrier (BBB) model

Authors: M. E. DONEGAN, C. A. SAVIC, M. K. LIVINGSTON, K. TOMOTOSHI, R. K. FIENE, *J. LIU, R. VAIDYANATHAN, C. B. CARLSON;
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Abstract: The blood-brain barrier (BBB) is a specialized network of cells that function to maintain a tightly controlled microenvironment around the brain. A robust BBB model is needed to evaluate barrier function, test drug permeability, and study how different diseases can affect it. Harnessing the power of iPSC technology, we were able to generate specific cell types of the human brain required to assemble such a model, including astrocytes, pericytes, & brain microvascular endothelial cells (BMEC). Importantly, the same donor iPSC line (01279) was used to make each of these cell types, yielding a fully isogenic tri-culture system. Marker expression and other cellular characterization data has been presented previously; therefore, we focused on the functional performance of the BBB model in various assay platforms. The traditional trans-endothelial electrical resistance (TEER) assay using cell culture inserts resulted in robust & reproducible signal (>1500 ohms▪cm^2) after 3 days. TEER measurements were further investigated using impedance-based instrumentation and barrier disruption with VEGF and mannitol was quantified. BBB permeability of fluorescent dextran molecules was assessed, and the apparent permeability of drug compounds (e.g., atenolol, caffeine, chlorpromazine, & propranolol) was quantified via LC-MS/MS. Generation of 3D spheres was accomplished using ULA plates and imaging revealed insightful structural features. Development of a receptor-mediated transcytosis assay was also initiated, beginning with characterization of transferrin receptor expression and evaluation of detection techniques. Finally, integration with emerging organ-on-a-chip technologies, such as MIMETAS OrganoPlate and Emulate Brain Chip, offers a unique way to further enhance biological complexity. Importantly, the keys to success here were consistency of supply made possible by differentiation at-scale resulting in large batches of cells, cryopreservation of all three cell types for subsequent on-demand use, and an optimized formulation of media/supplements to enable long-term survival. Taken together, this study highlights the modular and flexible nature of an isogenic human iPSC-derived BBB model as a new capability to advance the understanding of BBB function with respect to human health and disease.

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Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

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Program #/Poster #: PSTR283.12/II12

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH grant P30DA013429
NIH grant R01DA054921

Title: Role of Sigma-1R in modulating the blood-brain barrier permeability

Authors: J. L. BARR[1], E. BRAILOIU[1], S. INAN[1], E. M. UNTERWALD[1], ***G. C. BRAILOIU**[2];
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[2]Jefferson Col. of Pharm., Thomas Jefferson Univ., Philadelphia, PA

Abstract: Sigma-1R is an intracellular chaperone protein residing on the endoplasmic reticulum at the mitochondrial-associated membrane (MAM) region. Upon agonist stimulation, Sigma-1R dissociates from the complex with other proteins and translocates to the cell membrane where it regulates the function of receptors and channels, or to the nucleus where it regulates gene transcription. Sigma-1Rs are significant regulators of signaling, gene expression, and cell function in physiological conditions and disease states. We previously reported that Sigma-1R is expressed in rat brain microvascular endothelial cells (RBMVEC). We now investigated the role of Sigma-1R on blood-brain barrier permeability *in vitro* using Electric Cell-substrate Impedance Sensing (ECIS) and *in vivo*, using Evans Blue extravasation method and live imaging, in rats. RBMVEC were cultured on gold electrodes of ECIS arrays. Sigma-1R agonist PRE084 produced a dose-dependent reduction in RBMVEC monolayer resistance; the response was reduced by pretreatment with Sigma-1R antagonist BD-1047. *In vivo* assessment of BBB permeability indicates that PRE-084 increased dose-dependently the Evans Blue brain extravasation; the effect was reduced by the Sigma-1R antagonist, BD-1047. We also directly visualized brain microcirculation in the prefrontal cortex of awake rats with a miniature integrated fluorescence microscope (aka, miniscope; Doric Lenses Inc) and sodium fluorescein. Miniscope studies indicate that PRE-084 increased sodium fluorescein extravasation *in vivo.* Taken together, our results indicate that Sigma-1R activation increased the BBB permeability *in vitro* and *in vivo.*

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Poster

PSTR283. Blood-Brain Barrier

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Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01NS107342
NIH Grant R01NS114478

Title: Characterization and comparison of the blood-ganglion barrier in sympathetic versus sensory ganglia

Authors: *J. LI[1], R. KURUVILLA[2];
[1]Biol., [2]Johns Hopkins Univ., Johns Hopkins Univ., Baltimore, MD

Abstract: Proper neuronal function relies on selective barriers that maintain a homeostatic microenvironment of the nervous system. While barrier breakdown can lead to inflammation, neuronal damage, and potentially neurological diseases, an intact barrier can also be a challenge for therapeutic delivery. The blood-brain barrier (BBB) in the central nervous system (CNS) is well studied. However, the blood barrier in the peripheral nervous system (PNS) is poorly understood. In the PNS, the sympathetic nervous system controls the body's "fight or flight" response to stress and maintains body homeostasis, while the sensory nervous system is responsible for transmitting sensory information from the body to the brain. The cell bodies of sympathetic and sensory neurons are found in clusters called ganglia, where in addition to neuronal cell bodies, the ganglia contain non-neuronal cells including satellite glial and vascular cells. The goal of this study is to understand the structure and function of the blood-ganglion barrier (BGB) in sympathetic and sensory ganglia. Using tracer injections, we found that the permeability of blood vessels is different between sympathetic and sensory ganglia, with that in sensory ganglia being leakier than in sympathetic ganglia. The BBB function in the CNS is mainly conferred by endothelial cells with their specialized tight junctions and low level of transcytosis, as well as by other cell types, including pericytes and astrocytes, which contribute to barrier formation and maintenance. To identify the cellular and molecular bases for the differential vascular permeability between sympathetic and sensory ganglia, we are currently identifying the cellular unit of the BGB using whole mount immunostaining to label endothelial cells, pericytes, and satellite glial cells, the latter proposed to be analogous to astrocytes. We are assessing the expression and distribution of candidate tight junction proteins, including Claudin-5, ZO-1, and Occludin, which are known to be critical for BBB structure and function. We are also visualizing transcytosis in endothelial cells in peripheral ganglia using tracer injections and electron microscopy. Together, these studies will provide rare insight into the cell types and molecular mechanisms that define a blood barrier in peripheral ganglia, which will facilitate new treatments for pathologies that affect the peripheral nervous system.

Disclosures: **J. Li:** None. **R. Kuruvilla:** None.

Poster

PSTR283. Blood-Brain Barrier

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.14/II14

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: DSPAN F99-K00 NIH Grant 10393997

Title: The state-gate hypothesis: Key behavioral events and VTA activity predict rapid increases in local blood-brain barrier permeability

Authors: *S. FEKIR[1], K. TURNER[2], S. SCOTT[2], A. SHANKAR[2], E. KLEIN[2], B. R. GALLAGHER[3], C. DEISTER[2], Y. ZHAO[4], C. I. MOORE[2];
[1]Brown Univ., Pawtucket, RI; [2]Neurosci., Brown Univ., Providence, RI; [3]McGovern Inst. for Brain Research, Brain & Cognitive Sci., MIT, Cambridge, MA; [4]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Adaptive behavior depends on body state: The correct response to sensory inputs, and learning from decisions, requires a detailed understanding of current needs. Signals within vessels are a well-established source of such internal context, including hormonal, metabolic, and immunological indicators. However, the blood-brain barrier (BBB) is believed to sharply restrict such transmission, as sustained increases in permeability are a major health risk. Here, we test a resolution to these competing needs for information versus protection: **We predict the BBB is dynamic, providing increased access to body state at the time, and in Forebrain regions, where behaviorally relevant information is worth the risk.** This 'State-Gate' Hypothesis predicts that many brain systems that index relevance may exert such control. The Ventral Tegmental Area (VTA) is an ideal candidate, as its activity signals behavioral relevance and its axons closely encircle Forebrain vessels. We use 2-photon imaging, optogenetics and behavioral training to test this State-Gate/VTA-BBB Hypothesis. To track rapid changes in BBB permeability, we inject fluorescent molecules IV (e.g., 70kD Rhodamine B) and test if they are transmitted to parenchyma of mouse Primary Somatosensory Neocortex. **Our Preliminary Data supports this prediction**. During consolidation of a novel sensory association, **BBB permeability increases at cue onset and reward** (N = 3 mice). Axons from rostral VTA neurons ramify in SI (N=21 mice: Aransay et al., 2015). **Selective optogenetic activation (Chrimson) in these axons drives BBB permeability, and their endogenous calcium 'spikes' (GCaMP) predicts it** (N= 6 mice, 63 axons, 21,666 spikes). **Behavioral, optogenetic and spike-aligned data show similar rapid (> 250 ms) and discrete increases in permeability**, suggesting a common mechanism**.** In sum, in contrast to the common conception, we find the BBB responds rapidly, and is well-positioned to relay behaviorally relevant state information for integrated computations that produce adaptive behavior. These findings may have clinical import: In Alzheimer's Disease, mesocortical DA projections and the BBB are substantially altered: Failed communication between them may contribute to behavioral and health deficits. More generally, BBB compromise is central to many conditions, including addiction and sleep disorders, that are also associated with altered DA signaling.

Disclosures: S. Fekir: None. **K. Turner:** None. **S. Scott:** None. **A. Shankar:** None. **E. Klein:** None. **B.R. Gallagher:** None. **C. Deister:** None. **Y. Zhao:** None. **C.I. Moore:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.01/II15

Topic: F.07. Biological Rhythms and Sleep

Support: NSF GRFP
NIH grant HL149133

Title: Neural population dynamics in the midbrain and pons during sleep

Authors: *D. LOZANO, J. STUCYNSKI, S. CHUNG, F. WEBER;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Rapid eye movement (REM) sleep is characterized by a desynchronized electroencephalogram (EEG), muscle atonia, and vivid dreaming. The core circuits generating REM sleep are distributed throughout the brainstem and are composed of REM sleep-promoting (REM-on) and REM sleep-suppressing (REM-off) neurons. While much progress has been made in identifying specific neuronal populations that promote or suppress REM sleep, the neural dynamics that arise from the interactions between these REM regulatory populations and the dynamical mechanisms which gate transitions into REM sleep are largely unknown. We have previously demonstrated using optogenetic manipulations in mice that GABAergic neurons in the dorsomedial medulla (dmM) promote the induction of REM sleep via their projections to the dorsal and median raphe nuclei. To identify the neural dynamics within these downstream areas underlying NREM-to-REM sleep transitions, we employed Neuropixels probes to record the population activity in the dorsal and medial raphe, as well as neighboring midbrain and pontine brain areas, during spontaneous sleep in mice. We applied principal component analysis (PCA) to describe the population dynamics across the recorded brain regions. We found that the population activity during NREM and REM sleep is captured within low-dimensional subspaces. Furthermore we found that wakefulness, NREM, and REM sleep correspond to distinct areas along the trajectories traversed by the population activity within the PCA space. The REM sleep promoting effect of dmM stimulation largely resulted from an activation of REM-on and inactivation of REM-off neurons, effectively forcing the population activity towards REM sleep. Overall, these results demonstrate that the population activity during sleep in midbrain and pons areas are low-dimensional and provide a geometric description of how inputs from the REM promoting dmM neurons affect the population dynamics within these areas to induce NREM to REM sleep transitions.

Disclosures: D. Lozano: None. **J. Stucynski:** None. **S. Chung:** None. **F. Weber:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.02/II16

Topic: F.07. Biological Rhythms and Sleep

Support: National Science and Technology Innovation 2030 grant (2022ZD0206100)

Shanghai Municipal Science and Technology Major Project
(2018SHZDZX05 and 20JC1419500)
Lingang Laboratory grant (LG-QS-202203-01)

Title: Cortical regulation of two-stage REM sleep

Authors: *D. YUFAN[1], J. LI[1], M. ZHOU[1], Y. DU[2], D. LIU[1];
[1]Inst. of Neuroscience, CAS, Shanghai, China; [2]Arizona State Univ., Arizona State Univ., Tempe, AZ

Abstract: The sleep-wake cycle, including rapid eye movement (REM) sleep and non-REM sleep, are generally considered to be primarily regulated by distributed subcortical circuits, and cortical regions are involved in generating sleep-related EEG oscillations. However, recent studies showed that cortical neurons could be actively involved in non-REM sleep generation and homeostatic sleep regulation. Although cortical activation during REM sleep is considered to be associated with vivid dreaming, the global cortical dynamics and its role in regulating REM sleep remain unclear. Cortex-wide calcium imaging showed that REM sleep was accompanied by highly-patterned cortical activity waves, with the retrosplenial cortex (RSC) as a major initiation site. Two-photon imaging of layer 2/3 pyramidal neurons of RSC revealed two distinct patterns of population activities during REM sleep. These activities encoded two sequential REM sleep substages, characterized by contrasting facial movement and autonomic activity, and distinguishable EEG theta oscillation. Closed-loop optogenetic inactivation of RSC during REM sleep altered cortical activity dynamics and shortened REM sleep duration via inhibiting the REM substage transition. These results highlight a critical role of RSC in dictating cortical dynamics and regulating REM sleep progression.

Disclosures: D. Yufan: None. **J. Li:** None. **M. Zhou:** None. **Y. Du:** None. **D. Liu:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.03/II17

Topic: F.07. Biological Rhythms and Sleep

Support: ERC Starting Grant 639272
Research Council of Norway 274328
Research Council of Norway 231495

Title: Diverse, state-dependent modulation of local and long-range circuit elements in the retrosplenial cortex across the wake-sleep cycle

Authors: C. N. BERGE[1], E. HENNESTAD[1], K. VERVAEKE[1], A. R. CHAMBERS[2];
[1]Dept. of Mol. Med., Univ. of Oslo, Oslo, Norway; [2]Dept. of Otolaryngology, Head and Neck Surgery, Harvard Med. Sch., Boston, MA

Abstract: Across the wake-sleep cycle, cortical networks engage in large-scale oscillations associated with distinct cognitive functions. During active wakefulness (AW), theta rhythms organize hippocampal-cortical activity to support navigation. Quiet wakefulness (QW) and sleep support learning and memory via hippocampal sharp-wave ripples (SWRs), sleep spindles, and slow waves. Cortical circuits flexibly shift information processing regimes in a state-dependent manner, but the implementation of this at the cellular level is unclear. The retrosplenial cortex (RSC) is involved in state-dependent functions, e.g. sensory-motor processing, memory and sleep regulation, and receives a dense projection in layer 1 from the thalamus, which is implicated in state control. Due to the difficulty of measuring precise circuit activity across the wake-sleep cycle, it is not known whether state-dependent changes in RSC activity reflect thalamic inputs or are generated locally, and to what degree they differ by cell type. To explore this, we used two-photon calcium imaging and electrophysiology to monitor excitatory and inhibitory neurons and thalamic axons in RSC across the wake-sleep cycle in mice. We virally targeted GCaMP exclusively to the somata of local neurons and to thalamic axons in the superficial layers of RSC. A nuclear marker identified inhibitory neurons. We detected states/ oscillations via LFP, ECoG and EMG recordings from hippocampus, neocortex, and neck muscles, respectively. State dependence was most prominent in thalamic axons, with mean activity highest in AW and REM sleep, followed by QW and NREM sleep. L2/3 excitatory cells were not strongly state modulated on average, apart from decreased activity during REM. Inhibitory neurons displayed diverse average activity profiles across states. We also observed slow, within-state activity ramps, which could signal past or future state shifts. These ramps occurred in RSC neurons and thalamic axons to differing degrees. Finally, as large-scale oscillations can take place in different states—e.g. SWR in QW and NREM—we asked whether RSC is modulated primarily by state, oscillation, or both. Thalamic SWR responses were similar whether they were in QW or NREM. By contrast, SWR responses in RSC neurons exhibited state dependence. Ongoing analyses ask whether state- or oscillation- dependence changes over days in the same cells. In summary, thalamic axons convey a dense state-dependent activation to superficial RSC, but local neuron subtypes exhibit diverse modulation to states and oscillations across the sleep-wake cycle. This may underlie RSC's participation in diverse brain functions across states.

Disclosures: **C.N. Berge:** None. **E. Hennestad:** None. **K. Vervaeke:** None. **A.R. Chambers:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.04/II18

Topic: F.07. Biological Rhythms and Sleep

Support: ERC
SNF

University of Bern
Inselspital Bern

Title: Somato-dendritic decoupling in the Retrosplenial cortex neurons during REM sleep

Authors: M. BORSA, M. AIME, *A. ADAMANTIDIS;
Univ. of Bern, Bern, Switzerland

Abstract: Rapid eye movement (REM, also called paradoxical) sleep correlates with enhanced cellular activity in region-specific thalamo-cortical circuits and subcortical structures including the hippocampus, midbrain or hypothalamus. This REM sleep specific neuronal activity is hypothesized to promote structural plasticity and provide a window for the consolidation of contextual and emotional memories previously acquired during wakefulness, yet the underlying mechanism remains unclear. Amongst the cortical structures, the activity of neurons located in the retrosplenial cortex (RSC) is increased during REM sleep. Here we characterized the activity of RSC microcircuit across the sleep-wake cycle using simultaneous 2-photon calcium imaging and electrophysiological recordings in spontaneously head-restrained sleeping mice. We observed a REM sleep-specific reduction of pyramidal cell somatic activity concomitant to the activation of the interneurons expressing either parvalbumin (PV), somatostatin (SST) or vasoactive intestinal peptide (VIP). Furthermore, preliminary results showed a partial pyramidal somato-dendritic decoupling in REM sleep with an increase in local dendritic activities as compared to sporadic global events. Collectively, these observations suggested a region-specific fine-tuning of excitatory/inhibitory balance in RSC during REM sleep that may be involved in synaptic plasticity and contribute to information integration, memory consolidation and ultimately behavioural optimization.

Disclosures: M. Borsa: None. **M. Aime:** None. **A. Adamantidis:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR284.05/II19

Topic: F.07. Biological Rhythms and Sleep

Support: NIMH Grant 2R01MH113007

Title: Circadian control of dorsolateral bed nucleus of the stria terminalis ($BNST_{DL}$) via hypothalamic vasopressin (AVP) projections

Authors: *L. M. MONROY[1], S. H. OLSON[1], V. GRINEVICH[2], J. DABROWSKA[1];
[1]Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [2]Lab. of Neuropeptides, German Cancer Res. Ctr. and Central Inst. of Mental Hlth., Heidelberg, Germany

Abstract: The bed nucleus of the stria terminalis (BNST) is a limbic forebrain structure that regulates many physiological and behavioral processes, notably, fear and anxiety-like behaviors. The BNST receives inputs from many hypothalamic nuclei that regulate crucial physiological processes (water/electrolyte balance, temperature regulation, feeding, wake/sleep cycle). Our current studies demonstrate that hypothalamic hormone and neuromodulator arginine-vasopressin (AVP) has a direct excitatory effect on neurons in dorsolateral BNST ($BNST_{DL}$), particularly neurons expressing striatal-enriched protein tyrosine phosphatase (STEP). However, the source of specific peptidergic inputs containing AVP in the $BNST_{DL}$ are elusive. Hence, we used AVP-Cre transgenic rats (Cre-recombinase under the AVP promoter) injected with Cre-dependent pAAV hSyn Flex mGFP-2A-Synaptophysin-mRuby into the suprachiasmatic nucleus (SCN) or the supraoptic nucleus (SON) of the hypothalamus and we show that both these nuclei send AVP-containing inputs to the $BNST_{DL}$. To determine whether the SCN and $BNST_{DL}$ have synchronous activity, we quantified immunoreactivity patterns for AVP and STEP in the SCN and $BNST_{DL}$ across four zeitgeber times in rats housed in 12:12 light-dark cycles. We used STEP as an indirect marker of $BNST_{DL}$ neuronal inactivity. We found the highest AVP expression in the SCN occurred at ZT 11, which corresponded to the lowest STEP expression in $BNST_{DL}$ neurons, whereas the lower AVP expression in the SCN and higher STEP expression in $BNST_{DL}$ occurred at ZT 1. These results suggest that SCN-AVP and $BNST_{DL}$-STEP neurons show direct relationship, such as the higher AVP-SCN signals, the more active (expressing less STEP) $BNST_{DL}$ neurons are. We next used the Period2 Clock protein (PER2), a key gene of the circadian clock, to determine whether the SCN imposes circadian control over the $BNST_{DL}$. We found higher PER2 expression at ZT 1 in the $BNST_{DL}$ and SCN compared to PER2 expression at ZT 11. These results demonstrate an anatomical and functional connection between the SCN and $BNST_{DL}$ and have implications on how changing physiological conditions, in particular the wake/sleep cycle, through AVP prompt, can directly impact BNST activity and BNST-dependent fear- and anxiety-related behaviors.

Disclosures: L.M. Monroy: None. **S.H. Olson:** None. **V. Grinevich:** None. **J. Dabrowska:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR284.06/II20

Topic: F.07. Biological Rhythms and Sleep

Support: NHLBI Grant F31-HL-160451
NINDS Grant R01-NS-110865
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Eagle Autism Challenge Pilot Grant

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Hartwell Individual Biomedical Research Award

Title: Regulation of sleep and wake by corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus

Authors: *A. WIEST, S. CHUNG;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Sleep is characterized by transitions between different vigilance states: wake, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. As sleep has many beneficial and restorative effects, good quality sleep is important for mental and physical health. It has been well established that stress and sleep have a bidirectional relationship. Stress is known to be a major cause of disrupted sleep. Chronic sleep disruption can lead to an increased risk of developing psychiatric disorders. Studies have shown that there is a strong relationship between stress and impaired memory consolidation. Likewise, sleep disturbances can lead to memory impairments. The paraventricular nucleus of the hypothalamus contains corticotropin-releasing hormone (CRH^{PVN}) neurons that become activated by stress. Central or systemic administration of CRH induces wakefulness. While CRH has been implicated as a regulator of wakefulness, the role that CRH^{PVN} neurons play in the sleep-wake cycle after stress has not been fully investigated.We hypothesized that inhibition of CRH^{PVN} neurons during acute stress improves sleep and, subsequently, enhances performance on a hippocampus-dependent memory task. When mice were subjected to acute restraint stress, NREM and REM sleep were significantly decreased while wake was increased within the first few hours following the stress. When CRH^{PVN} neurons were inhibited during restraint stress, NREM and REM sleep percentages were increased and wake percentage was decreased compared to restraint stress only control mice. Because sleep is crucial for memory, we also tested memory consolidation with a hippocampus-dependent task, spatial object recognition. Mice that underwent restraint stress after training had impaired memory performance. However, mice with CRH^{PVN} inhibition during restraint stress after training performed better on the memory task. Thus, inhibition of a population of wake-promoting, stress-active neurons during restraint stress improved sleep and reversed memory consolidation deficits seen after restraint stress.

Disclosures: **A. Wiest:** None. **S. Chung:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.07/II21

Topic: F.07. Biological Rhythms and Sleep

Support: UCLA Department of Integrative Biology & Physiology Hyde Fellowship
REM Sleep & Behavior R01 Grant #MH060670

Title: Estrous cycle dependent changes in transient oscillation dynamics during sleep in the hippocampus and cortex of adult female rats

Authors: *R. JANG[1], G. R. POE[2];
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]Dept. of Integrative Biol. and Physiol., UCLA Chapter, Los Angeles, CA

Abstract: In mature female rats, the estrous cycle is characterized by fluctuating progesterone and estrogen hormones which are known to influence cognitive function, processing of emotionally salient memories, and sleep. Work from our lab has shown that sleep architecture and features of sleep critical for memory consolidation, such as slow oscillations and spindles, are modulated by the phase of the estrus cycle in a brain region-dependent manner. We sought to build on prior work by using the Dynamic Oscillations (Dynam-O) toolbox to characterize time-frequency coupling dynamics of local field potentials across the estrus cycle in females. We used slow oscillation power as the objective measure of sleep depth, enabling characterization of sleep as a continuous time-varying process as opposed to restricting analyses to discretized states. *We hypothesized that females would show changes in the density of transient oscillatory events coupled to slow oscillation (SO) power in an estrous cycle dependent manner.*
Four adult female rats were implanted with electrodes in the CA1 region of the hippocampus and medial prefrontal cortex and recorded across sleep and wake. Estrous cycle tracking was performed by histological determination. Distinct time-frequency (TF) peaks from the spectrogram were detected using the MATLAB implementation of the watershed method in the Dynam-O toolbox. Individual TF-peaks in the 4-25 Hz range were identified for all animals across each phase of the estrus cycle using recordings from the first 6-hours of the lights-on period. Within this range, clear theta and spindle events were observed. The density (# events/min) and proportion of TF-peak occurrences remaining after noise removal (~2% of peaks) were analyzed relative to power and phase of SO events (0.3-1.5 Hz) to generate TF-power and TF-phase histograms. We then compared high hormone (HH) vs low hormone (LH) days. We found distinct regions of the SO power histograms correspond to sleep/wake states when compared to sleep staging by an expert scorer. Additionally, density of events that are coupled to the SO varied by frequency in an estrous phase and brain region dependent manner. For example, when compared to LH, in the HH condition the hippocampus showed decreased while the cortex showed increased spindle (10-16 Hz) density during NREM sleep. Furthermore, they were differentially coupled to SO phase such that the hippocampus showed greater spindle coupling at the SO-trough, while the cortex showed enhanced coupling at the SO-peak. Further research is needed to explore how these time-frequency dynamics influence learning and memory across the estrus cycle.

Disclosures: R. Jang: None. **G.R. Poe:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

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Program #/Poster #: PSTR284.08/II22

Topic: F.07. Biological Rhythms and Sleep

Support: NIMH grant 1R01MH135565
NINDS grant 1R01NS118440

Title: Cholinergic modulation of network dynamics during NREM and REM sleep and their differential roles during sleep consolidation

Authors: M. SATCHELL[1], D. MCKINSTRY[2], S. ATON[4], *M. ZOCHOWSKI[3];
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Abstract: Across vertebrate species, sleep states are known to cycle consistently from non-rapid eye movement (NREM) to REM sleep. However, the functional significance of these transitions is unknown. We use a simplified biophysical network model to show that state-specific changes in cholinergic signaling during NREM and REM sleep can mediate dramatic changes in network activity patterns and subsequently can play differential and critical role in sleep dependent memory consolidation. Specifically, we show that the sequential, bidirectional changes in cholinergic neuromodulation during these sleep states plays a vital role in consolidation, particularly when multiple memory traces are being stored simultaneously. In the low-ACh (NREM-like) state, the inhibitory interneurons regulating the activity of the principal cells are less active leading to network disinhibition and allowing for rapid recruitment of new cells into the memory engram, and their consequent enlargement. In the subsequent high-ACh (REM-like) state, ACh mediates activation of these interneurons that competitively suppress activity among newly recruited excitatory pyramidal neurons during prior NREM, leading to the orthogonalization of newly enhanced representations of different memory traces. We observe analogous suppression experimentally when Medial Septum cholinergic cells are activated optogenetically during NREM. We further find that, in the in silico model, this iterative sequence of state-specific activations during NREM/REM cycling is essential for memory storage in the network, serving a critical role during simultaneous consolidation of multiple memories. These results are contrasted to NREM-like only and, separately, REM-like only sleep.

Disclosures: M. Satchell: None. **D. McKinstry:** None. **S. Aton:** None. **M. Zochowski:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.09/II23

Topic: F.07. Biological Rhythms and Sleep

Support: R01 NIMH 60670

Title: Different simultaneous sleep states in the hippocampus and cortex are associated with learning and memory in rodents

Authors: *W. PETTIBONE[1], C. ALDACO[2], K. SWIFT[5], B. T. RILEY[6], J. J. EMRICK[7], A. M. WIKENHEISER[3], G. R. POE[4];
[1]NSIDP, [3]Psychology, [4]Dept. of Integrative Biol. and Physiol., [2]UCLA, Los Angeles, CA; [5]Mol. and Integrative Physiol., Walter Reed Army Inst. of Res., SILVER SPRING, MD; [6]Columbia Basin Col., Pasco, WA; [7]BMSP, Univ. Michigan, Ann Arbor, MI

Abstract: Sleep has long been assumed to be both unitary and global, that is, sleep states inferred from one region of the brain are thought to be representative of all other regions. Recent work has demonstrated that the brain may, in fact, be in multiple sleep states at once. Given the prominent role of sleep in many types of learning and memory consolidation, this novel asynchronous sleep phenomenon may play a role in how sleep helps to shape behavior and accommodate learning. We trained Long-Evans rats on four tasks: a motor learning task (the complex ladder), two spatial hippocampal tasks (the hidden goal task and the eight-box maze), and a cue-based striatal task (the light-cued circular maze), each over the span of seven days. Rats completed all seven days of one task before proceeding on to the next. On all four tasks, rats demonstrated continuous behavioral learning over the course of each week: markedly increased performance initially, followed by a gradual plateau. We recorded the rats' sleep simultaneously in motor cortex, hippocampus, and prefrontal cortex. Each recording channel was subsequently analyzed to determine sleep state. Asynchronous sleep was defined as any epoch in which at least one region was in a different sleep state than any other region. We found that, at baseline, asynchronous sleep comprised approximately 50% of total sleep time on average. There was no significant difference in the time each region spent in each stage. Asynchronous sleep initially increased as the rats learned each task, before settling back to a level close to baseline. Number of bouts of asynchronous sleep similarly increased and then declined. Rats that had a greater change in asynchronous sleep demonstrated improved performance on the task the next day. In the eight-box maze, hippocampal REM increased ($p < 0.05$, $n = 10$); in the rest of the tasks, the region-specific results remain to be assessed. These findings suggest that learning may be enhanced or modulated by different sleep states in an asynchronous manner.

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Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.10/II24

Topic: F.07. Biological Rhythms and Sleep

Support: AMED JP21zf0127005
CREST JPMJCR1655

Title: The population of GABAergic neurons in the ventrolateral periaqueductal gray is implicated in the occurrence of cataplexy in narcoleptic mice.

Authors: *S. JEONG[1,2], S. UCHIDA[2], S. SOYA[1,2], T. SAKURAI[1,2];
[1]Univ. of Tsukuba, Tsukuba / Ibaraki, Japan; [2]Intl. Inst. for Integrative Sleep Med. (WPI-IIIS), Tsukuba, Japan

Abstract: Cataplexy is characterized by sudden episodes of muscle atonia during wakefulness, often triggered by intense positive emotions, and is associated with the loss of orexin-producing neurons. It has been regarded as an abnormal intrusion of rapid eye movement (REM) sleep into wakefulness. Recent research has revealed the involvement of that glutamatergic neurons in the sublaterodorsal tegmental nucleus (SLD), especially those projecting to the ventromedial medulla (VMM) (referred to as $Glu^{SLD\rightarrow VMM}$ neurons), in muscle atonia during both cataplexy and REM sleep.By utilizing the cell-type-specific TRIO (cTRIO) method in *vGlut2-IRES-Cre* mice, we identified the upstream input neurons of $Glu^{SLD\rightarrow VMM}$ neurons, including those in the ventrolateral periaqueductal gray (vlPAG), deep mesencephalic nucleus (DpMe), and various other brain regions. These findings suggest that these neurons may play a role in the neural circuit underlying cataplexy and REM atonia.The vlPAG is known to be crucial in the regulation of REM sleep. However, its precise involvement in cataplexy remains incompletely understood. To address this, we conducted optogenetic activation of GABAergic neurons in vlPAG of narcoleptic mice. We injected Cre-dependent AAV carrying SSFO-eYFP into the vlPAG in *vGAT-IRES-Cre;orexin-ataxin3* male mice and stimulated these neurons with blue light during wakefulness. The activation increased the propensity of transitioning into cataplexy-like episodes (CLEs). To confirm whether the SLD acted as the downstream target of vlPAG GABAergic neurons, we optogenetically activated axons of vlPAG GABAergic neurons by implanting optic fibers into the SLD. This manipulation also increased the probability of inducing CLEs. Notably, these cataplexy-related effects were not observed when performing the same optogenetc manipulation of the vlPAG or its axons in non-narcoleptic mice. Taken, together, these observations suggest that there is a population of vlPAG GABAergic neurons that positively regulate the occurrence of cataplexy in midbrain region, acting as upstream regulators of SLD neurons. Although these findings appear to contradict previous research indicating an inhibitory role of the midbrain region in the regulation of REM sleep or cataplexy, these observations suggest that there may be specific regulation mediated by diverse populations within the ventrolateral periaqueductal gray (vlPAG).

Disclosures: **S. Jeong:** None. **S. Uchida:** None. **S. Soya:** None. **T. Sakurai:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.11/Web Only

Topic: F.07. Biological Rhythms and Sleep

Support: Swiss Nation Science Foundation Grant 84759
Etat de Vaud (Switzerland)

Title: A role for interoceptive vGluT2-expressing neurons in the jugular-nodose ganglion of the left vagus nerve in the regulation of sleep architecture and spectral composition

Authors: *N. CHERRAD[1], A. OSORIO-FORERO[2], R. CARDIS[1], Y. EMMENEGGER[1], L. M. FERNANDEZ[1], P. FRANKEN[1], A. LUTHI[1];
[1]Univ. of Lausanne, Lausanne, Switzerland; [2]Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: When awake, external sensory stimuli and bodily sensations determine how we perceive our surroundings. Once asleep, we disconnect from the sensory environment and react poorly to external stimuli. However, little is known about how interoceptive stimuli are processed by the sleeping brain. The vagus nerve is a mixed sensory-motor nerve that interfaces between the autonomic periphery and the central nervous system. We asked whether stimulating specifically vagal sensory afferents modulates sleep. To address this question, we decided to use viral transfection techniques to enable a sustained chemogenetic activation of vGluT2-expressing neurons in the jugular-nodose ganglion of the left vagus nerve, in combination with polysomnographic, local field potential (LFP), thermistor, fiber photometry, in freely moving conditions after low (1.5mg/kg i.p.) or high (2.5mg/kg i.p.) CNO injections or NaCl at ZT0. Whole-cell patch-clamp recordings confirmed that our viral transfection approach targetted functional vagal glutamatergic synaptic contacts in the brainstem nucleus tractus solitarius. We found that chemogenetic activation of the vagal sensory afferents suppressed rapid-eye-movement sleep (REMS) in its major spectral and autonomic correlates in a dose-dependent manner. The REMS onset latency was increased from 13±2min after NaCl injection to 82±16min after low-dose (Wilcoxon-sign-rank-test, $p=4.8e^{-4}$, n=11) to 185±27min after high-dose CNO injection (Wilcoxon-sign-rank-test, $p=2.4e^{-4}$, n=11). Moreover, heart rate remained decelerated throughout the period during which REMS was not detectable. In contrast to the suppression of REMS, the spectral properties of non-REMS were moderately affected, with evidence for a minor increase in low-frequency power (delta (1.5-4Hz) (n=11, $p=1.8e^{-4}$, Student's-t-test) and slow oscillations (0.5-1.5Hz) (n=11, $p=6.6e^{-4}$, Student's-t-test) and a decrease in sigma (10-15Hz) power (n=11, $p=1.5e^{-4}$, Student's-t-test) after a low dose of CNO. To characterize more comprehensively the physiological correlates of sleep during elevated vagal activity, we measured the cortical brain temperature and found a drop in temperature (-4.3±3°C, n=7) after vagal sensory stimulation. The mechanisms underlying these alterations are currently being addressed using fiber photometry techniques in combination with LFP recordings. Our findings point to a major role for sustained vagal afferent activity in body-brain physiology in the balanced between non-REMS and REMS. Moreover, they indicate that vagus nerve stimulation could offer non-invasive strategies to improve sleep architecture in pathological conditions.

Disclosures: **N. Cherrad:** None. **A. Osorio-Forero:** None. **R. Cardis:** None. **Y. Emmenegger:** None. **L.M. Fernandez:** None. **P. Franken:** None. **A. Luthi:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR284.12/II25

Topic: F.07. Biological Rhythms and Sleep

Support: Swiss National Science Foundation Grant 84759
Etat de Vaud

Title: Locus coeruleus activity fluctuations set a non-reducible time frame for mammalian NREM-REM sleep cycles.

Authors: *G. FOUSTOUKOS[1], A. OSORIO-FORERO[2], R. CARDIS[1], N. CHERRAD[1], C. DEVENOGES[1], L. FERNANDEZ[1], A. LUTHI[1];
[1]Univ. of Lausanne, Lausanne, Switzerland; [2]Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: The noradrenergic locus coeruleus (LC) is both wake- and sleep-active. While the LC supports vital brain functions during wakefulness, it can both promote and disrupt sleep, leaving its roles for sleep unclear. Here, we show that the LC is essential for the progression of undisturbed sleep because it creates a non-reducible time frame for the non-rapid-eye-movement (NREM) sleep-REM sleep cycle. Fiber-photometric jGCaMP8s-based LC activity measures, closed-loop optogenetics and mouse sleep-wake monitoring revealed that LC showed ~50-s-activity fluctuations, of which high levels promoted NREMS and occasional spontaneous arousals, while low levels permitted NREMS-to-REMS-transitions. LC high activity prevented precocious REMS entries in the undisturbed NREMS-REMS cycle, and LC fluctuations spaced repeated REMS entries to no shorter than ~50-s-intervals during REMS restriction. A stimulus-enriched wake experience strengthened LC fluctuations, which contributed to subsequent NREMS fragmentation and delayed REMS. The LC fluctuations hence constitute a fundamental time interval for the NREMS-REMS cycle, but they can become sleep-disruptive as a result of prior wake experience.

Disclosures: G. Foustoukos: None. **A. Osorio-Forero:** None. **R. Cardis:** None. **N. Cherrad:** None. **C. Devenoges:** None. **L. Fernandez:** None. **A. Luthi:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.13/II26

Topic: F.07. Biological Rhythms and Sleep

Support: Independent Research Fund Denmark 3101-00373A
Lundbeck Foundation R413-2022-622

Title: Altered locus coeruleus activity during sleep leads to age-related cognitive decline

Authors: V. N. COMPERE[1], M. ANDERSEN[1], A. TSOPANIDOU[2], T. RADOVANOVIC[2], M. NEDERGAARD[2], ***C. KJAERBY**[1];
[1]Ctr. for Translational Neuromedicine, [2]Univ. of Copenhagen, Copenhagen, Denmark

Abstract: As we age, cognitive abilities as well as the quality of sleep decline. Sleep disturbances frequently precede the onset of dementia in neurodegenerative diseases and include an excessive number of micro-arousals. We and others recently demonstrated a link between micro-arousals and the norepinephrine (NE)-producing neurons of the locus coeruleus (LC), whereby periodic LC activity maintains and shapes memory consolidating NREM sleep domains. Interestingly, loss of LC neurons is reported both in aging and neurodegeneration and remaining LC neurons display altered functionality. In this project, we wanted to test the hypothesis that age-related LC dysfunction leads to cognitive decline through compromised regulation of memory consolidating NREM sleep domains. To answer this question, electroencephalograms (EEG) and electromyograms (EMG) recordings were combined with fiber photometric measures of NE and optogenetic manipulations of the LC in aged mice. We demonstrated that older mice display hippocampus-dependent cognitive decline and altered sleep composition in comparison to healthy young adult control mice. Furthermore, aged mice were less responsive to manipulations of the LC-NE system indicating reduced dynamics of the system. The less responsive LC-NE system was implicated in cognitive deficits, since LC manipulations during sleep could boost memory in young, but not old animals. These findings pave the way for future therapeutic investigations focusing on restoring sleep heterogeneity in the elderly generation to improve healthy aging.

Disclosures: V.N. Compere: None. **M. Andersen:** None. **A. Tsopanidou:** None. **T. Radovanovic:** None. **M. Nedergaard:** None. **C. Kjaerby:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.14/II27

Topic: F.07. Biological Rhythms and Sleep

Support: Max Planck Society
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EMBO

Title: Evidence for a central pattern generator (CPG) controlling the ultradian sleep cycle

Authors: *L. FENK, J. L. RIQUELME, G. LAURENT;
Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: Sleep is ubiquitous in the animal kingdom, yet our understanding of its possible functions, its control and evolution, remains rudimentary. Two main sleep states have traditionally been distinguished in mammals – rapid-eye-movement (REM, also *paradoxical* or

"*dream sleep"*) and slow-wave (SW, also non-REM) sleep – but biphasic sleep is widespread, also exists in birds (Ookawa and Gotoh, 1964) and non-avian reptiles (Shein-Idelson, Ondracek et al., 2016; Libourel et al., 2018), and was recently reported in fish (Leung et al., 2019), suggesting a possibly common origin. Studying sleep in the Australian dragon *Pogona vitticeps*, we have previously described a reptilian homologue of the mammalian claustrum and its role in generating activity patterns characteristic of SW sleep (Norimoto, Fenk et al., 2020). By recording from the two claustra bilaterally, we then showed that claustrum activity is precisely coordinated across the midline during REM, but not during SW sleep, revealing a fundamental difference in inter-hemispheric coordination during the two main phases of sleep (Fenk et al., 2023). Exploring the possible identity and functional properties of circuits that could underlie the generation of the ultradian sleep cycle, we now provide evidence supporting the existence of a central pattern generator (CPG)-type circuit driving the regular alternation between SW and REM. Specifically, exploiting the accessibility of key brain structures together with the extreme regularity and short duration of the *Pogona* sleep cycle (~120 sec at room temperature, compared to 90-100 min in humans), we reveal two hallmarks of CPG circuits described in other systems: (1) phase-resetting in response to a phasic input, in conjunction with a clear phase dependence of the effectiveness of this perturbation in causing a phase delay or advance, respectively, and (2) entrainment of an identical rhythm in the awake state, in response to a regular sensory drive whose statistics match those of the natural sleep rhythm. These results are consistent with the existence of a CPG-type circuit driving the ultradian sleep rhythm, and lend support to early studies in mammals suggesting the existence of oscillator circuits in the brainstem (Kleitman, 1963; McCarley and Hobson, 1975).

Disclosures: L. Fenk: None. **J.L. Riquelme:** None. **G. Laurent:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.15/II28

Topic: F.07. Biological Rhythms and Sleep

Support: JSPS-22F22106
Hirose foundation 2023

Title: Crf neurons in the latera lpart of the interstitial nucleus of the anterior commissure promote wakefulness

Authors: *C. HUNG[1], S. UEDA[1], S. M. RAHAMAN1[1], M. YAMAMOTO[1], N. FUKATSU[1], S. TAKEMOTO-KIMURA[1], A. YAMANAKA[2], D. ONO[1];
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Abstract: Sleep and wakefulness are regulated by numerous factors, such as stress and physiological illness. Among various stressors, novel environmental induces an acute pattern of sleep disturbances similar to stress-induced insomnia in humans. However, it remains unclear how the novel environment affects sleep and wakefulness. To clarify, we performed c-Fos staining after exposure to the novel environment. We found that the number of c-Fos positive neurons was increased in several brain regions, such as corticotropin-releasing factor (CRF)-producing neurons in the paraventricular nucleus (PVN), the lateral part of the interstitial nucleus of the anterior commissure (IPACL). CRF, a key stress-responsive molecule, has been previously shown to promote wakefulness through PVN-CRF neurons. Thus, we focused on investigating the role of IPACL-CRF neurons in sleep and wakefulness. To investigate the function of IPACL CRF neurons in sleep and wakefulness, we employed the designer receptors exclusively activated by designer drugs (DREADD) system via viral injection, and vigilance states were assessed using electroencephalography (EEG) and electromyography (EMG). Our results revealed that the activation of IPACL-CRF neurons increased wakefulness. Inhibiting these neurons did not affect sleep/wakefulness, but reduced novel-environment-induced wakefulness. These results suggest that IPACL-CRF neurons promote wakefulness under novel environments. Further experiments are necessary to clarify how the IPACL-CRF neurons promote wakefulness.

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Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.16/JJ1

Topic: F.07. Biological Rhythms and Sleep

Title: Characterization of Sleep/Wake and EEG Spectral Patterns in Chrna4 and Chrna5 Null Mutant Mice

Authors: *H. L. MATHEWS[1], J. A. STITZEL[2], S. AKI[3], M. BROWN[3];
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Abstract: The sleep/wake cycle is a complex process involving numerous brain regions and neurotransmitter systems. The cholinergic system is involved in the promotion of cortical arousal and the initiation and modulation of REM sleep. Little is known about the contribution of nicotinic cholinergic receptors (nAChRs) in sleep and wakefulness. The present study examined the sleep/wake cycle and EEG spectral patterns in male C57BL/6J (C57), and genetically null mutant mice for either Chrna4 [α4(-/-)] or Chrna5 [α5(-/-)]. Relative to C57 mice, both α4(-/-) and α5(-/-) had decreased NREM sleep during the active phase (AP). Conversely, α4(-/-) showed increased REM during the inactive phase (IP) compared to C57 mice. The most robust finding with regard to the sleep/wake cycle was the observation of increased sleep fragmentation in α4(-

/-) mice compared to both C57 and α5(-/-) mice. This effect was observed during both phases. When examining individual sleep states, NREM sleep in α4(-/-) was severely fragmented during both phases, while REM sleep was only affected during the IP. These results suggest a role of α4(-/-) in NREM sleep consolidation during both phases, and a role of α4(-/-) in REM sleep consolidation during the IP only. Several between genotype differences were also observed in EEG spectral patterns. Significant findings include decreased relative theta rhythms (4.10-8.00hz) during REM in α4(-/-) compared to C57 and α5(-/-) mice, compensated by non-significant increases in relative Beta (15.01-30.00Hz) and Gamma (30.01-50.00Hz). Findings for Gamma rhythms are perhaps the most interesting. During wake, gamma rhythms were consistently but non-significantly reduced in α5(-/-) compared to both C57 and α4(-/-); during NREM, gamma rhythms were increased in α4(-/-) compared to both C57 and α5(-/-) mice, this effect was significant at ZT20-23; and during REM, gamma rhythms were significantly decreased in both α4(-/-) and α5(-/-) at all time points relative to C57 mice. These observations suggest a role of α4 and α5 in the generation of gamma rhythms that is state dependent. Cumulatively, these findings inform on the individual role and function of the α4 and α5 nAChRs in the generation and maintenance of sleep, wakefulness, and brain wave spectral frequencies.

Disclosures: **H.L. Mathews:** None. **J.A. Stitzel:** None. **S. Aki:** None. **M. Brown:** None.

Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

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Program #/Poster #: PSTR284.17/JJ2

Topic: F.07. Biological Rhythms and Sleep

Support: 1R01EB029852-01
1RF1NS118442-01

Title: A non-oscillatory, millisecond-scale embedding of brain state provides insight into behavior

Authors: *A. M. SCHNEIDER[1], D. F. PARKS[2], K. B. HENGEN[3];
[1]Washington Univ. in St. Louis, St. Louis, MO; [2]Univ. Of California Santa Cruz, Santa Cruz, CA; [3]Biol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Sleep and wake are understood to be slow, long-lasting processes that span the entire brain. Brain states correlate with many neurophysiological changes, yet the most robust and reliable signature of state is enriched in rhythms between 0.1 and 20 Hz. The possibility that the fundamental unit of brain state could be a reliable structure at the scale of milliseconds and microns has not been addressable due to the physical limits associated with oscillation-based definitions. Here, by analyzing high resolution neural activity recorded in 10 anatomically and functionally diverse regions of the murine brain over 24 h, we reveal a mechanistically distinct

embedding of state in the brain. Sleep and wake states can be accurately classified based in 10^0 to 10^1 ms of neuronal activity sampled from 100 μm of brain tissue. In contrast to canonical rhythms, this embedding persists above 1,000 Hz. This latent fast embedding is robust to substates and nested neurophysiological events. To ascertain whether such fast and local structure is meaningful, we leveraged our observation that individual circuits intermittently switch states independently of the rest of the brain. Brief state discontinuities in subsets of circuits correspond with brief behavioral discontinuities during both sleep and wake. Our results suggest that the fundamental unit of state in the brain is consistent with the spatial and temporal scale of neuronal computation, and that this resolution can contribute to an understanding of cognition and behavior.

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Poster

PSTR284. Sleep Mechanisms: Circuits and Systems

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Program #/Poster #: PSTR284.18/JJ3

Topic: B.07. Network Interactions

Support: NIH Grant 5R01HD078220
NIH Grant R37HD091280

Title: Connectivity Map of the Habenulo-Interpeduncular Pathway

Authors: *K. ARIYASIRI[1], J. CHENG[1,2], J.-H. CHOI[1,3], A. SUBEDI[2], M. E. HALPERN[1,2,3]; [1]Mol. and Systems Biol., Dartmouth Col., Hanover, NH; [2]Dept. of Biol., Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Embryology, Carnegie Inst. for Sci., Baltimore, MD

Abstract: Connectivity Map of the Habenulo-Interpeduncular Pathway
Krishan Ariyasiri[1 #], Ji Cheng[1,2 #], Jung-Hwa Choi[1,3], Abhi Subedi[2], Marnie E. Halpern[1,2,3 #]
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The habenulo-interpeduncular pathway is a highly conserved conduction system in the vertebrate brain, that is present from primitive fish to humans. Neurons in the bilaterally paired dorsal habenulae (dHb) predominantly innervate an unpaired midbrain target, the interpeduncular nucleus (IPN) through the fasciculus retroflexus fiber bundles. The habenular nuclei influence a wide range of behaviors, from sleep and reward to fear and anxiety and have been a recent focus in research on addiction. Despite increasing functional studies, our knowledge of the neuronal properties, organization, and connections of the dHb and IPN is limited. We identified transcripts enriched in the dHb by performing RNA-seq on dHb dissected from adult zebrafish brains relative to the remaining tissue. Comparison with a single-cell transcriptomics dataset, together

with customized cluster analysis, enabled generation of a hierarchical transcription profile for dHb neurons. We then performed RNA in-situ hybridization to confirm spatial patterns of expression in larval and adult fish. Through the adoption of the QF/QUAS binary transcriptional regulatory system and CRSIPR/Cas9 targeted genomic integration, we successfully recovered transgenic QF driver lines for newly identified dHb-expressing genes. Axonal endings of labeled dHb neuronal subpopulations were mapped to specific target regions along the dorsoventral extent of the IPN using genes for membrane-tagged fluorescent reporters under QUAS control. On the basis of overlap between dHb clusters, we can predict the patterns of IPN innervation for additional neuronal subtypes. Together, the transgenic and computational approaches provide a more complete map of dHb-IPN connectivity in the zebrafish brain.

Disclosures: K. Ariyasiri: None. **J. Cheng:** None. **J. Choi:** None. **A. Subedi:** None. **M.E. Halpern:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.01/JJ4

Topic: F.07. Biological Rhythms and Sleep

Support: NIH Grant MH104606

Title: The temporal dynamics of aperiodic activity track changes in sleep structure

Authors: M. AMEEN[1], ***J. JACOBS**[2], K. HOEDLMOSER[1], T. DONOGHUE[2];
[1]Univ. of Salzburg, Salzburg, Austria; [2]Columbia Univ., New York, NY

Abstract: Electrophysiological data has an aperiodic (1/f-like) property whereby power decreases as a function of increasing frequency. The degree of this decay, which can be measured as the aperiodic exponent (or the 'spectral slope'), has been shown to relate to states of consciousness. Here, we further investigate aperiodic activity across sleep stages, extending the methodological approaches to address limitations of previous work, including a) the use of simplified estimation-models (examining a narrow frequency range with a simple model form) and b) low temporal resolution. To address these limitations - which can miss features and dynamics that occur over a broader frequency range and/or a short time frame - we explored changing the frequency range and complexity of the model used to estimate aperiodic activity, as well as applying these models in a time-resolved manner to track features with and between sleep stages. We analysed both an intracranial electroencephalography (iEEG) dataset (n=91) from human patients sleep scored into non-rapid eye movement (NREM; stages N2 and N3) and rapid eye movement (REM) sleep, as well as a high-density EEG dataset collected from 17 healthy humans across a full night of sleep. Spectral features were estimated using the specparam toolbox (formerly 'fooof'), comparing model-forms and computing time-resolved estimates. We show that switching from the narrowband frequency range (30-45Hz) that has been used in sleep

literature to a broader frequency range improves the model performance. Further, using a more complex model from that incorporates the knee frequency, i.e., the frequency at which the slope of the power spectrum changes, revealed that stage-dependant changes in the spectral exponent of the iEEG data is driven by a change in the knee frequency. Finally, in the EEG signal, we were able to demonstrate temporally resolved estimates of aperiodic activity whose time courses differentiated transitions to between sleep stages (comparing, for example, transitions from N2 to N3 from transition from N2 to N1). Overall, our results show that aperiodic activity during sleep tracks changes in sleep (micro-) structure, and that this can be characterized by expanding the model complexity and temporal resolution of the applied methods. Through this project, we also propose updated guidelines for the estimation of aperiodic activity in neural data that, based on the findings here, can lead to better characterization of electrophysiological signals leading to improved quantifications that can be used to examine relationships between neurophysiological signals and behavioural states of interest.

Disclosures: **M. Ameen:** None. **J. Jacobs:** None. **K. Hoedlmoser:** None. **T. Donoghue:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.02/JJ5

Topic: F.07. Biological Rhythms and Sleep

Support: NIH Grant R01-GM109086
NIH Grant R01-DC04290

Title: Identifying hidden states of consciousness during sleep using multivariate autoregressive models

Authors: X. LIU[1], B. M. KRAUSE[1], K. V. NOURSKI[3], ***M. I. BANKS**[1], B. D. VAN VEEN[2]; [1]Anesthesiol., [2]Electrical and Computer Engin., Univ. of Wisconsin, Madison, WI; [3]Neurosurg., The Univ. of Iowa, Iowa City, IA

Abstract: Stages of sleep identified by standard polysomnography are superpositions of actual consciousness states. For example, during deep sleep, humans transition between unconsciousness (UC) and disconnected consciousness (DC, dreaming). Previous studies also showed that the brain exhibits different electrophysiological activity during different sleep stages and consciousness states. However, how to identify those consciousness states is still an open question. Here, we developed a novel sequential multistate multivariate autoregressive (SM-MVAR) model clustering algorithm. SM-MVAR uses a Gaussian mixture model to assign data segments to one of several MVAR models representing different conscious states. The MVAR models are learned from the data as part of an iterative assignment process in which segments are assigned to the most likely model, the models are re-estimated from the assigned segments, and the iterative reassignment process continued until the assignments do not change. We divided

multichannel human intracranial electrophysiological data recorded during sleep into short 4-second segments. Each segment was labeled by sleep stage (W, i.e., wake, N1, N2, N3, and REM) obtained using standard polysomnography. We then applied the SM-MVAR algorithm to those segments with the assumption that four consciousness states exist during sleep: two states of connected consciousness (CC+, i.e., awake and alert, and CC-, i.e., awake but drowsy and inattentive), disconnected consciousness (DC, i.e., dreaming), and unconsciousness (UC). We initialized the MVAR models by assigning N3 segments to UC, REM segments to DC, W segments to CC+, and N1 segments to CC-. We then ran the algorithm to iteratively update the assignments and MVAR models. We compared the classification of data segments into consciousness states with standard polysomnography, and the results suggest our method could capture transitions among consciousness states during sleep at high temporal resolution. We also performed 4-fold cross validation on our SM-MVAR algorithm and found that our algorithm could stably reveal the underlying clusters of data segments. Directed connectivity derived MVAR model coefficients revealed changes in network structure that may underlie transitions between consciousness states. Overall, we believe our method has broad utility for identifying hidden states in any multichannel system that can be reasonably approximated by MVAR models and specifically to gain mechanistic insights into the neural correlates of consciousness.

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Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.03/JJ6

Topic: F.07. Biological Rhythms and Sleep

Support: Ministerial grant
ANR

Title: Is paradoxical sleep a paradoxical state of sleep?

Authors: *F. BOSCHER[1], N. URBAIN[2];
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Abstract: Paradoxical sleep (PS), coined as such by Jouvet in 1959 for the striking resemblance of its electroencephalogram (EEG) to the one observed during the fundamentally different cognitive state of wakefulness, is characterized by muscular atonia and the occurrence of rapid eye movements. Recently, this has led to a distinction between two substates: phasic (during eye movements) and tonic PS. In mice, we also observed whisker movements during PS. The

whisker system therefore offers the unique opportunity to study cortical and thalamic modifications associated with whisker movements in both wakefulness and PS.
We performed extra- and intracellular recordings of thalamic cells in head-fixed mice, combined with local field potential (LFP) recordings in the primary somatosensory (S1) and motor (M1) cortices, while simultaneously monitoring the EEG, the electromyogram and the whisker movements with a high-speed camera.
Whisker movements (whisking) in PS occurred significantly more toward the end of the episodes and differed from whisking in wakefulness by a higher frequency of protraction/retraction cycles and a lower amplitude. On the EEG, they were associated with an increase in the mean Theta (5 - 12 Hz) wave frequency as well as an increase in Gamma (60 - 90 Hz) power. On S1-LFP, whisking was associated with a significant decrease of Delta (2-6Hz) power in both wakefulness and PS. While this Delta activity seemed widely distributed across the cortex (EEG, S1-LFP, M1-LFP) in quiet wakefulness, it appeared restricted to S1 during PS. Remarkably, we also observed spindles oscillations in the S1-LFP during PS, but only outside whisking periods. In the sensory thalamus, whisking was associated with an increase in the firing rate, in both wakefulness and PS. In addition, 49% (18/37) of the recorded cells modified their firing pattern during whisking in PS: while they fired bursts of action potentials outside whisking, typical firing pattern of thalamic cells during SWS, they switched to a tonic activity during whisking. Interestingly, we also observed during PS membrane potential oscillations in the spindle frequency range in a subset of thalamic cells (n=3 out of 6), like in SWS.
Taken together, our results show that a substate of PS, outside phasic events, bears clear SWS characteristics, opening a new insight on the function of PS.

Disclosures: **F. Boscher:** None. **N. Urbain:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

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Program #/Poster #: PSTR285.04/JJ7

Topic: F.07. Biological Rhythms and Sleep

Support: NRF grant 2015R1D1A1A02061486
NRF grant 2019R1A2C1009674

Title: Changes in the core architecture of brain network during propofol-induced unconsciousness in human ECoG

Authors: *M. CHOE[1], S.-H. JIN[1], J. KIM[1], C. CHUNG[2];
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Abstract: Since consciousness is upheld through communication in the brain network, its characteristics should change as consciousness emerges and disappears. The k-core percolation is

a way to describe the core structure of the brain network by eliminating peripheral structures of the network. In the present study, we investigated the core structure changes of the brain network during the propofol-induced unconscious state using human electrocorticography (ECoG).We recruited 4 medically intractable epilepsy patients (4 females; age: mean = 27.3, SD = 6.4 years) with ECoG monitoring. Conscious ECoG was acquired in the ward or operating room with subjects' eyes closed without any stimuli. Unconscious ECoG was acquired after the subject lost the ability to respond to verbal commands with general anesthesia using the target-controlled infusion of propofol and remifentanil. The average recording time during conscious and unconscious states was 113.4 seconds (standard deviation, 63.1 seconds). The ECoG data during conscious and unconscious states were segmented into 10-s epochs having 50% overlap. The complex Morlet wavelet transform with a wave number of 2.48 was applied for time-frequency analysis. We estimated the power correlation for functional connectivity using the Pearson correlation coefficient. We calculated the correlation matrix of each frequency band of interest (delta: 1-3 Hz, theta: 4-7 Hz, alpha: 8-12 Hz, beta: 13-30 Hz, low gamma: 30-90 Hz, high gamma: 90-140 Hz). We constructed the adjacency matrix using the threshold of 40%. We estimated k-maximum core structures and the number of nodes in cortical regions of k-maximum core structures using k-core percolation. We computed the regional difference of k-maximum core structures between conscious and unconscious states using Wilcoxon signed rank test ($p < 0.05/8$).Compared to the conscious state, the number of k-maximum core nodes decreased in the frontal region, whereas the number of k-maximum core nodes increased in the posterior regions during the propofol-induced unconscious state. The reconstruction of core structure in the brain network with increased coreness in posterior regions and decreased coreness in the frontal region would be associated with states of consciousness.

Disclosures: **M. Choe:** None. **S. Jin:** None. **J. Kim:** None. **C. Chung:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.05/JJ8

Topic: B.07. Network Interactions

Support: Department of Mathematics and Statistics at Boston University
Center for Systems Neuroscience at Boston University

Title: Broadband coupling to slow wave phase during propofol-induced unconsciousness reflects both spiking and non-spiking dynamics at the cortical surface

Authors: *P. F. BLONIASZ[1], J. TAUBER[3], S. BRINCAT[4], E. K. MILLER[4], E. P. STEPHEN[2]; [1]Grad. Program For Neurosci., [2]Mathematics and Statistics, Boston Univ., Boston, MA; [3]Brain and Cognitive Sci., [4]The Picower Inst. for Learning and Memory, MIT, Cambridge, MA

Abstract: Propofol, a gamma-aminobutyric acid (GABA) potentiating anesthetic, is a widely used agent to induce unconsciousness in clinical settings. Several electroencephalographic (EEG) indicators of propofol-induced unconsciousness (PIU) have been reported, including widespread slow oscillations, a frontal alpha rhythm, and phase amplitude coupling (PAC) between the phase of the slow wave (0.1 Hz - 4 Hz) and broadband amplitude (5-50 Hz; Purdon et al., 2013; Stephen et al., 2020). The slow wave-broadband PAC indicator has been shown to occur on more posterior electrodes when participants initially become unconscious, but later becomes ubiquitous across both frontal and posterior electrodes as the dose of propofol increases. Thus, PIU is thought to comprise at least two discrete unconscious brain states that are distinguishable at the level of scalp EEG signals. Furthermore, the broadband PAC indicator was hypothesized to reflect up- and down-states in spiking activity at the cortical surface, predicting that propofol may influence cortical spiking activity differently in frontal vs posterior brain areas. Hence, there is a pressing need to characterize the cortical counterparts of the broadband-slow wave phase PAC observed in EEG. Here, we establish a broadband-slow wave paradigm in non-human primates using chronic Utah arrays to record local field potential (LFP) and multiunit spiking data from two macaques (Bastos et al. 2021). PAC was calculated via two different analyses that were based on 1) the mean vector PAC between the instantaneous slow wave phase and broadband amplitude of LFP data and 2) the generalized linear model-based prediction of broadband power as a function of slow wave basis functions. It was found that, like human scalp indicators of PIU, there are discrete brain states defined by dose-dependent broadband-slow wave coupling across brain regions. Additionally, it was found that cortical spike times coincide with elevated broadband power, but changes in broadband power can occur in the absence of detected spikes - suggesting that broadband can contain more complete local network information than multiunit spiking. We observe systematic changes in spectral shape and slope as a function of the slow wave phase, which we interpret in terms of local excitatory and inhibitory tone.

Disclosures: P.F. Bloniasz: None. **J. Tauber:** None. **S. Brincat:** None. **E.K. Miller:** None. **E.P. Stephen:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.06/JJ9

Topic: B.07. Network Interactions

Title: Monitoring and predicting brain states in unresponsive patients with EEG-and machine learning-based approaches in the intensive care unit

Authors: *L.-M. KRUMM[1], C. MEISEL[2];
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Abstract: Prognosticating for patients with Disorders of Consciousness (DOCs) is a complex process due to their diverse etiologies and pathophysiologies. However, advancements in the field of Machine Learning (ML) and the increased availability of long-term EEG and multimodal data, supported by comprehensive data warehouses, may provide improved methods for monitoring and prognosticating DOCs. We here propose to address the complexity of DOCs by assessing the divergence of a patient's EEG from what may be considered 'normal', and to detect long-term trends for prognostication over time. Specifically, we employ deep autoencoders (AE) to map normal healthy EEG signals and deviations from it into latent space. For healthy normal EEG signals we use publicly available datasets (Temple University Hospital (TUH) dataset) and datasets covering different vigilance states (Cleveland Family Study sleep dataset). To estimate differences from normal in latent space we use three datasets: the TUH slowing and seizure dataset (dataset 1), a dataset from patients with a diverse set of DOCs obtained from the intensive care unit (DOC defined as Glasgow Coma Scale Score < 9, dataset 2), and a long-term EEG dataset from patients during recovery from cardiac arrest (dataset 3). Using these data, we employ three different methodological approaches: a unimodal data approach (using only EEG powerbands), a bimodal data approach (using correlation measures between pairs of EEG channels), and a raw EEG time-series data approach (without predetermined data features). All AE approaches are benchmarked to simpler machine learning approaches, including logistic regression classifiers. We use the Rand index as a metric to quantify how well the data is clustered in latent space. Initial results indicate that power spectral densities features provide the best clustering in latent space for normal, seizure, and slowing EEG data.Our results indicate that AE can capture EEG dynamics in latent space relevant for prognostication of DOCs across diverse etiologies and pathophysiologies. Our ultimate goal is to develop a data processing pipeline with the best-performing algorithm for prospective bedside application. By continuously monitoring the brain states of ICU patients with respect to distance from normal, healthy dynamics, we aim to identify long-term trends that can enhance prognostication.

Disclosures: **L. Krumm:** None. **C. Meisel:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.07/Web Only

Topic: B.07. Network Interactions

Support: CIHR

Title: Age-related changes in EEG during isoflurane-induced surgical anesthesia

Authors: *P. SOJA[1], ***P. SOJA**[2], T. MARIAM[1], R. TADAVARTY[1];
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Abstract: We recently reported that during protracted periods of isoflurane anesthesia (IA), the cortical EEG signature of male but not female adult rats revealed oscillatory behavior characterized by high-power up state and low-power down states (Soja *et al., Soc. Neurosci. Abstracts*, 2018, 125.04/H4). The present study investigated whether similar EEG dynamics occurred in old (~18 months, n=11) *vs.* adult (4 - 6 months, n= 13) male rats. Cortical EEG activity was recorded bilaterally (S1) using stainless steel electrodes under IA (1.0-1.25%). The concentration of isoflurane was adjusted to keep the animals' EEG activity at a stable surgical anesthetic plane characterized by delta wave activity. A tagging procedure was used to identify the onset and offset of up states. The tagged EEG states were then re-constructed as continuous up and down state EEG records. Age-related differences occurred in the number and spectral features of the up *vs.* down states. Adult rats averaged 11 up-state oscillations/hr that lasted ~6.3 min while aged rats revealed ~4.5 up-state oscillations/hr lasting ~6.6 min. Relative power differences between up and down states were assessed in δ (1-4 Hz), θ (5-8 Hz), α (9-12 Hz) and β (13-25 Hz) bandwidths. Adult rats revealed ~30% decrease and ~48 % increase in relative power values for δ and θ bands, respectively when comparing up *vs*. down states. In old rats, a ~ 33% decrease and 20% increase in power values occurred in δ and θ bands, respectively when up *vs*. down states were compared. Power in the α band increased by ~69 %, and ~53% in adult *vs.* old rats, respectively when up *vs.* down states were compared. These findings demonstrate distinct differences in EEG activities between adult and old male rats during prolonged periods of surgical IA. The functional consequence of these age-related differences in EEG oscillations requires further investigations.

Disclosures: P. Soja: None. **P. Soja:** None. **T. Mariam:** None. **R. Tadavarty:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.08/JJ10

Topic: F.07. Biological Rhythms and Sleep

Support: Countering Existing Threats – Repurposing Acquisition and Investigation of Drugs for Repurposing program sponsored by the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense through IAA A2010021021AH0040

Title: Determining a sedative dose of dexmedetomidine in the African green monkey

Authors: J. MORGAN[1], T. WHITTY[1], G. CAPACIO[1], D. CRAIG[1], B. TRAVIS[1], *H. MCCARREN[2];
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Abstract: Dexmedetomidine (DEX), an α2-adrenergic receptor agonist, is frequently used in combination with other drugs to induce sedation in non-human primates (NHPs). DEX has proven especially useful for imaging studies, where it acts as an anesthetic-sparing agent to improve functional MRI signal. All published protocols in which DEX is used as a sole sedative agent have been performed in rhesus macaque monkeys. This project sought to determine an intravenous (IV) sedation protocol for DEX in African Green monkeys (AGMs). Ten AGMs were fitted with steel collars, removed from their home cage using pole capture, and placed in a restraint chair, where an intravenous catheter was placed in their saphenous vein. DEX was infused at a fixed rate via syringe pump, and the AGM was monitored for signs of sedation and changes in heart rate and blood pressure. The rate and cumulative dose of DEX infusion was adjusted between AGMs until an infusion rate and duration was identified that consistently led to ~15 minutes of hand grip loss accompanied by a mean arterial pressure (MAP) that remained >45mmHg throughout the infusion. An infusion of 10 μg/kg of DEX at 40 μg/kg/hr met this criteria. Signs of sedation observed included markedly reduced muscle tone, loss of grip, yawning and brief periods of eye closure. At this infusion rate (n = 6), loss of hand grip response occurred 9.3 ± 2.1 minutes (mean ± SD) after initiation of infusion. Animals that received a total of 10 μg/kg (n = 3) lost hand grip for 14.3 ± 0.6 minutes. All 10 animals were able to return to their home cages without incident after a brief period of recovery in the chair. DEX has a strong safety profile and a broad therapeutic index, but bradycardia and hypotension are important potential complications. The AGMs that received the optimized DEX dosing protocol in this study maintained MAP in a safe range, with minimum MAP measurements ranging from 73-77 mmHg. This illustrates that AGMs can be successfully sedated with DEX short-term, with minimal detrimental cardiac effects.
Disclaimers: The views and opinions of authors expressed herein do not necessarily state or reflect those of the Department of Army, Department of Defense, or the U.S. Government and shall not be used for advertising or product endorsement purposes. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense (USAMRICD), and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, the Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.

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Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.09/JJ11

Topic: F.07. Biological Rhythms and Sleep

Support: FAER-MRTG 2023 Spring Cycle

Title: Discovering neuronal firing patterns underneath slow waves: a novel approach in rodent models of anesthesia and sleep

Authors: A. IYER[1], J. RYU[4], G. LI[4], T. BAI[4], M. ZHAO[2], F. ZHAN[3], T. H. SCHWARTZ[3], H. MA[3], H. FANG[4], ***J.-Y. LIOU**[1];
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Abstract: Slow waves are prominent features of pharmacologically-induced general anesthesia, characterized by oscillatory local field potentials and neuronal activities that are separated into UP and DOWN states. These slow waves bear a resemblance to those observed during deep non-rapid eye movement sleep. Yet, the debate regarding the similarity of underlying neuronal firing patterns that constitute the slow waves in both brain states persists. This study presents a novel approach to address this longstanding controversy. Our approach combines 'transparent electrodes,' embedded in a PDMS film, with a specialized transgenic mouse strain that expresses GCaMP6f sparsely at superficial cortical layers. This combination allows us to capture individual neuronal activity over a large cortical area while recording the spatiotemporal structures of slow waves. Importantly, our technique enables ultrafast high-speed calcium imaging, faithfully capturing neuronal spikes throughout the entire dorsal neocortex along with local field potentials. This facilitates the differentiation of large-scale spatiotemporal features of slow waves with fine resolution. By employing our unique approach, we achieve a comprehensive characterization of the neuronal firing patterns associated with cortical slow waves under various conditions. This enables us to compare natural sleep with general anesthesia induced by isoflurane and dexmedetomidine, which induce slow waves via drastically different mechanisms. Additionally, our approach allows versatile cortical stimulation paradigms that reveal distinct signatures of neuronal and local field activity closely linked to consciousness states, as evaluated from a behavioral perspective. In summary, our study introduces an innovative methodology that combines electrophysiological and optical techniques, allowing for high spatiotemporal resolution recordings of neuronal activity across a large cortical area during slow waves. By shedding light on the similarities and differences between anesthetic-induced and natural sleep-related slow waves, our findings contribute to a deeper understanding of the mechanisms underlying general anesthesia and sleep states.

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Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.10/JJ12

Topic: B.07. Network Interactions

Support: NIH Grant K99GM141450

Title: Simultaneous calcium imaging and electrophysiology in the rat cortex during sleep and general anesthesia induced by diverse agents

Authors: *E. D. MELONAKOS[1], R. P. FISHER[2], E. D. WHITT[2], I. J. LAMBERT[2], K. D. HAAS[2], K. K. MCCORMACK[2], M. W. TSAI[2], K. VINCENT[2], M. J. SIEGMANN[2], K. SOLT[1], E. N. BROWN[3], C. J. NEHS[1];
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Abstract: Sleep and many general anesthetics, including propofol, ketamine, and dexmedetomidine, cause profound slow waves (0.5-4 Hz) in the cortical field potential. These slow waves reflect widespread, synchronous oscillations between depolarized and hyperpolarized membrane voltages of nearby neurons and may be important for preventing consciousness. Although the molecular targets of propofol, ketamine, and dexmedetomidine are known, it is unknown whether their respective slow waves are generated in the same way at the neural circuit level. Moreover, whether the slow waves of these anesthetics share a common mechanism with the slow waves of sleep remains unknown. Previous research from our lab showed that the efficacy of brainstem stimulation to reduce anesthesia-induced slow waves depends on the anesthetic's molecular target, suggesting distinct slow wave mechanisms. We tested this hypothesis in 6-8 month old female Sprague Dawley rats by using a miniscope to record calcium transients from individual neurons in the prelimbic cortex of the prefrontal cortex (PFC) during sleep and administration of general anesthetics. Simultaneously, we recorded electrophysiological signals (EEG/LFP) near the imaged area of the PFC. Finally, for each condition (sleep or anesthetic), we observed the relationship between the activity of individual neurons and the electrophysiological signal by plotting vectors of unity length at each calcium event's respective slow wave phase. Then, we calculated the mean vector for each neuron and found the mean of all neurons' mean vectors for a given rat/condition (the mean vector of the rat).We found variability in both the strength of slow wave phase-locking (the radius of the mean vector of the rat) and the preferred (mean) slow wave phase between rats and between conditions. For two rats with three conditions each, we found the following mean vectors [phase (rads), radius]: Rat 1, sleep, [-1.98, 0.15]; Rat 1, dexmedetomidine, [-2.18, 0.07]; Rat 1, propofol, [-0.71, 0.08]; Rat 2, sleep, [1.24, 0.13]; Rat 2, dexmedetomidine, [0.85, 0.05]; Rat 2, propofol, [-0.19, 0.19]. While different phase preferences were seen among the rats for a given condition, the preferred phase of dexmedetomidine was closer to that of sleep than propofol within both rats. These early results may indicate a greater degree of similarity in cortical activity during sleep- and dexmedetomidine-induced slow waves than sleep- and propofol-induced slow waves.

Disclosures: E.D. Melonakos: None. **R.P. Fisher:** None. **E.D. Whitt:** None. **I.J. Lambert:** None. **K.D. Haas:** None. **K.K. McCormack:** None. **M.W. Tsai:** None. **K. Vincent:** None. **M.J. Siegmann:** None. **K. Solt:** None. **E.N. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pascall Systems, Inc.. **C.J. Nehs:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.11/JJ13

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01GM141792-01

Title: Whole Brain Network Changes During Propofol-induced Unconsciousness

Authors: *X. CHEN[1,2], S. R. CRAMER[3], N. ZHANG[2];
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Abstract: The altered level of consciousness induced by general anesthetics is associated with various dynamic changes in whole brain communication. Previous studies have identified the altered neural electrical activity using electrophysiology (ephys) recording during loss of consciousness. However, ephys signal can only provide information about regional changes, leaving the brain-wide communication during this process largely unknown. To investigate the whole-brain functional alteration during loss of consciousness, we simultaneously recorded electrophysiology-fMRI (ephys-fMRI) signal from six rats during propofol-induced loss of consciousness, verified by the test of loss of righting reflex (LORR). We found the power of low frequency-band ephys data exhibit a sudden increase within a narrow time window when animals lost consciousness. Brain network-level changes were assessed using the whole-brain fMRI signals during the same time window. This study provides data revealing global brain network level changes during the process of loss of consciousness.

Disclosures: X. chen: None. **S.R. Cramer:** None. **N. Zhang:** None.

Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.12/JJ14

Topic: B.07. Network Interactions

Support: Human Brain Project-SGA3 grant agreements N. 945539
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Title: Brain state modulation of cortical network topography: the role of the retrosplenial cortex

Authors: *F. RESTA[1], A. SCAGLIONE[2], F. S. PAVONE[3];
[1]Univ. of Florence, Sesto Fiorentino, Italy; [2]Univ. di Firenze, Sesto Fiorentino, Italy; [3]LENS, LENS, Sesto Fiorentino, Italy

Abstract: Large-scale cortical dynamics play a role in many cognitive functions such as goal-directed behaviors, motor learning, and sensory processing. The spatiotemporal patterns of neuronal activity across multiple brain regions undergo substantial alterations during different brain states, including wakefulness and anesthesia. Although there is considerable knowledge regarding the overall changes in neuronal firing and synchronization in different brain states, the specific network topography engaged remains less understood. The aim of this work was to identify the cortical networks modulated by the anesthesia level. To achieve this goal, we employed the GroupICA analysis method on widefield mesoscale imaging recordings. This approach enabled us to identify spatially independent components (ICs) that represent elements of cortical networks shared among subjects as the anesthesia level decreased from deep anesthetized towards the awake state. Our findings revealed a marked dependence of ICs associated with the retrosplenial cortices on brain state. These ICs were most prominent during deeper levels of anesthesia, while they were less prevalent during the awake state. Analysis of IC occurrence unveiled a strong correlation between the retrosplenial cortices during deeper anesthesia states, which diminished as anesthesia lightened. In summary, our results indicate that coactivation of the posterior-medial cortices predominates over other connectivity patterns during deeper anesthesia levels, whereas a more rich repertoire of dynamics is expressed in lighter anesthesia and in the awake state.

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Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.13/JJ15

Topic: F.07. Biological Rhythms and Sleep

Support: Jane Coffin Childs Fund

Title: A single nucleus transcriptomic approach to understand the neuronal encoding of homeostatic sleep pressure and anesthesia

Authors: *L. J. ELIAS[1], H. KHOO[2], S. C. HUR[2], J. RIHEL[3], S. BLACKSHAW[4];
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London, United Kingdom; [4]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Disordered sleep is a widespread health problem, yet how the brain homeostatically regulates sleep, driving a pressure to sleep after prolonged wakefulness, is poorly understood. To identify neurons that encode sleep pressure, I used single nucleus RNA sequencing to observe transcriptional changes in sleep deprived (SD) vs rested larval zebrafish forebrain. The small size of the larval zebrafish brain, conserved sleep wake machinery, large clutch sizes for high throughput behavioral assays, and transparent larval state make the zebrafish an excellent system in which we can address these questions. To control for any effects driven by the method of sleep deprivation (e.g. arousal or stress from gentle handling), I conducted the same analysis in *sik3* Sleepy mutants, a genetic model of high sleep pressure. I have identified a cluster of neurons, marked by *tac1*, that exhibits *th* upregulation in both in the *sik3* mutant compared to wild type controls, as well as in sleep deprived compared to rested controls. Secondly, I observe a widespread reduction in *RAMP1* in forebrains of SD vs rested control and in *sik3* mutant compared to wt controls. To experimentally induce sleep pressure in zebrafish, we employ sleep deprivation techniques such as gentle handling with a paintbrush. This method is not ideal, as it 1) limits the number of experimental animals; 2) does not allow simultaneous behavioral tracking; 3) introduces red light for visibility during the dark cycle; and 4) is taxing on the experimenter, limiting SD duration to 4-6 hours. Therefore, I have developed a high throughput and automated method of sleep deprivation by applying randomized water pulses to individual larvae while simultaneously tracking their behavior. I have successfully induced sleep pressure with this approach, observing a rebound sleep in the hours following the pulses. Sleep pressure is dissipated by rebound sleep, but whether an anesthesia-induced sleep-like state can dissipate sleep pressure is unclear, varying with organism and type of anesthesia. Understanding the neuronal basis of how anesthesia controls consciousness could help us distinguish circuits for sleep pressure vs loss of consciousness. By coupling single nucleus transcriptomics with HCR fluorescent *in situ* hybridization, I identified a cluster of telencephalic neurons, marked by *tac3b*, that respond with immediate early gene upregulation to diverse anesthetics, including tricaine, isoflurane, and benzocaine. Together these preliminary datasets lay the groundwork to understand the neuronal encoding of sleep pressure and anesthesia.

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Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.14/JJ16

Topic: B.07. Network Interactions

Support: NIH Grant R35 GM145319
NIH Grant R01 GM121457

Title: Neuron-class specificity of volatile anesthetic action in C. elegans

Authors: *A. S. CHANG[1], C. W. CONNOR[2], C. V. GABEL[1];
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[2]Anesthesiol., Brigham and Women's Hosp., Boston, MA

Abstract: The mechanism of action of the volatile anesthetics at the molecular and local neuronal network level have yet to be thoroughly explicated. Through the implementation of high-speed volumetric whole nervous-system imaging in *C. elegans*, our previous work has characterized how exposure to isoflurane, a commonly used volatile anesthetic, results in breakdown of neuron-to-neuron communication. However, the question remains whether particular neuronal sub-populations are more sensitive to volatile anesthetic-induced breakdown, and if patterns of suppression of neuronal communication in distinct sub-populations can characterize observed differences in shallow and deep anesthesia. In this study, we address this question through the implementation of a fluorescent marker system (NeuroPAL) to identify neurons within the simple and completely mapped C. elegans nervous system. Single neuron-resolution calcium imaging was performed on *C. elegans* (n=10) under awake conditions, and during exposure to levels of atmospheric isoflurane analogous to light and moderate anesthesia in mammals. Identified neurons were assigned to presynaptic-postsynaptic pairs based on previously characterized synaptic maps of the *C. elegans* connectome. Synaptic pairs were then sorted by presynaptic neurotransmitter identity: acetylcholinergic, glutamatergic, GABAergic, and aminergic. We found that under light anesthesia acetylcholinergic neurons displayed decreased synaptic pair correlation ($n = 405$, $p = 0.002$, paired sample t-test) and reduced mean signal power ($n = 160$, $p < 0.001$), while other neuron sub-populations were largely unaffected. Under moderate anesthesia, acetylcholinergic synaptic pairs exhibit significant correlation suppression ($n = 270$, $p < 0.001$) as do glutamatergic synaptic pairs ($n = 184$, $p = 0.01$) and aminergic synaptic pairs ($n = 102$, $p = 0.002$). Interestingly, we additionally observed suppression of correlation between pairs of neurons known to be linked by gap junctions under both light ($n = 183$, $p=0.002$) and moderate ($n = 100$, $p < 0.001$) Anesthesia. These findings show that some distinct populations of neurons are indeed more sensitive to volatile anesthetics than others. Our results specifically implicate acetylcholinergic synapses, and potentially gap junctions, as being the most sensitive to volatile anesthetics and thus the potential initiating points of anesthetic action. Greater depths of anesthesia may then be characterized by an increasing cohort of affected neuron types.

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Poster

PSTR285. States of Consciousness: Sleep States, Anesthesia, and Sedation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.15/JJ17

Topic: F.07. Biological Rhythms and Sleep

Support: Simons Foudnation

Title: Detecting Sleep and Wake with Frequency-Based Algorithms Using Ambulatory EEG Devices

Authors: *M. HACOHEN[1], G. EYLON[2], I. DINSTEIN[3];
[1]Ben-Gurion Univ., Beer-Sheva, Israel; [2]Ben-Gurion university, Beer-Sheva, Israel; [3]Ben Gurion Univ., Beer Sheva, Israel

Abstract: Objectives: To develop an automated pipeline that can filter out various EEG noise sources and classify sleep and wake segments throughout an overnight EEG recording using an ambulatory wireless EEG device. **Background**: Sleep and wake differ in their neural activity patterns as evident in EEG recordings. During wakefulness the cortex is dominated by fast oscillations of low amplitude, and conversely, when sleep begins, cortex becomes dominated by slow oscillations of high amplitude. Despite these dramatic changes in cortical activity, there are few trusted algorithms for detecting sleep onset and final awakening. Here we demonstrate the accuracy of an algorithm that utilizes the ratio between alpha and theta bands to identify sleep onset and final awakening. **Design/Methods**: Data was collected from three adult men over a period of three consecutive weeks (total of 80 nights) using commercially available wireless EEG headbands (Dreem Inc.). We developed an algorithm for automated detection of noise originating from movements, muscle contractions, and poor electrode impedance. Specifically, the algorithm detected noisy EEG epochs according to their variance, skewness, kurtosis, mobility, and complexity. After extracting noisy segments, the algorithm detected the top 20 consecutive 30-second epochs that had the highest delta power (i.e., slow wave sleep), which are expected to indicate the first sleep cycle. The algorithm then identified sleep onset by moving backwards in time and detecting the last epoch with an individually defined alpha/theta ratio. Final awakening was identified as the last epoch of the recording with the same alpha/theta ratio. **Results**: The accuracy and robustness of the algorithm was evaluated by comparing its results to manual scoring. The algorithm labeled sleep onset times did not differ significantly from those labeled manually ($t(79)=1.34$, $p = 0.18$), with the algorithm exhibiting a mean bias of 2 minutes. Similarly, algorithm labeled final awakening times did not differ significantly from those labeled manually ($t(79)=1.4$, $p = 0.9$), with the algorithm exhibiting a mean bias of 0.3 minutes. Comparison of the algorithm with the Dreem staging showed a significant difference in sleep onset detection (($t(79)=5.16$, $p = 0.01$), with the algorithm exhibiting a mean bias of 10 minutes. In contrast, final awakening times did not differ significantly from those scored by Dreem ($t(79)=-1.3$, $p = 0.2$), with the algorithm exhibiting a mean bias of 2 minutes. **Conclusions**: The developed pipeline offers a useful approach for analyzing large datasets of sleep EEG recordings even when collected with wireless ambulatory EEG devices.

Disclosures: M. Hacohen: None. **G. Eylon:** None. **I. Dinstein:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.01/Web Only

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH BHTP T32 AG078114

Title: Apolipoprotein E genotype impacts murine skeletal muscle mitochondrial coupling efficiency in a late-onset Alzheimer's disease model

Authors: *C. JOHNSON[1], C. LYSAKER[1], C. S. MCCOIN[1], V. DRUMMOND[1], R. KEMNA[1], E. FRANCZAK[1], A. BLANKENSHIP[1], C. S. JOHN[1], X. CAO[1], M. E. MORRIS[1], J. P. THYFAULT[1], H. M. WILKINS[1], P. C. GEIGER[1], J. K. MORRIS[2];
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Abstract: Apolipoprotein ε4 (*APOE4*) is the greatest genetic risk factor for Alzheimer's disease (AD). *APOE4* carriers who are obese are at even greater risk of developing AD. This human condition is replicated in *APOE4* targeted-replacement (TR) mice, with high-fat diet (HFD) reducing spatial memory compared to *APOE3* TR mice. Further, *APOE4* genotype increases risk for developing diabetes and cardiovascular disease, conditions that alter bioenergetic function in skeletal muscle. Interestingly, lipid-driven mitochondrial respiration is reduced in muscles of individuals in the early stages of cognitive decline. Despite this, the impact *APOE4* has on muscle metabolism and the role this would play in modifying AD susceptibility is unclear. Here, we sought to determine if *APOE4* modulates lipid metabolism in muscle in response to a HFD. We used 8-month old male and female *APOE4* (n=13) and *APOE3* (n=15) TR mice on a C57BL/6 background fed a low-fat diet (LFD) or HFD for 4 months prior to sacrifice. Lipid-driven mitochondrial oxygen consumption was measured in isolated mitochondria from quadriceps muscle using high-resolution respirometry (Oroboros Oxygraph-2k). Coupling efficiency was calculated from basal and state 3 (ADP-stimulated) respiratory states. Western blot was used to quantify the expression of gastrocnemius muscle proteins involved in lipid metabolism, including apolipoprotein E (APOE), fatty acid binding protein 4 (FABP4) and carnitine palmitoyl transferase 1B (CPT1B). Basal and state 3 mitochondrial oxygen consumption in muscle are not affected by genotype or diet. However, *APOE4* reduced coupling efficiency compared to *APOE3* ($p=0.012$), regardless of diet. There was no effect of genotype on the expression of lipid metabolizing proteins measured. However, HFD increased muscle APOE ($p<0.001$) and FABP4 ($p<0.001$) expression, and resulted in a trending elevation in CPT1 ($p=0.077$) expression compared to LFD-fed mice. Reduced mitochondrial coupling efficiency in *APOE4* mouse muscle suggests reduced pairing of lipid-driven oxygen consumption to ATP synthesis. Reduced coupling and oxidative stress is a hallmark of aging muscle. Current ongoing studies are being conducted to determine the relationship between coupling efficiency and the production of reactive oxygen species. The lack of genotype-driven effects on protein expression suggests that differences in lipid handling by *APOE* genotype occurs independently of changes in the expression of key metabolic proteins measured in this study. Further studies are needed to determine the mechanism underlying differences in lipid-driven coupling efficiency and the impact this has on muscle and brain health.

Disclosures: **C. Johnson:** None. **C. Lysaker:** None. **C.S. McCoin:** None. **V. Drummond:** None. **R. Kemna:** None. **E. Franczak:** None. **A. Blankenship:** None. **C.S. John:** None. **X. Cao:** None. **M.E. Morris:** None. **J.P. Thyfault:** None. **H.M. Wilkins:** None. **P.C. Geiger:** None. **J.K. Morris:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.02/JJ18

Topic: F.08. Food and Water Intake and Energy Balance

Support: Samsung Science and Technology Foundation under Project Number SSTF-BA2001-09

Title: How do parabrachial Pdyn+ neurons monitor ingestion?

Authors: M. KIM[1,2], ***D.-J. KOO**[1,3], G. HAN[1,2], H. CHO[1,2], D.-Y. KIM[1], G. HEO[1], S.-Y. KIM[1,4,3];
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Abstract: Mechanosensory feedback from the digestive tract to the brain ensures that animals consume appropriate amounts of food and water. Our group previously found that neurons in the parabrachial nucleus expressing the prodynorphin gene (hereafter PB^{Pdyn} neurons) are activated during ingestive behavior, as well as mechanical probing of the oropharyngeal cavity, esophagus, and stomach (Kim *et al*., Nature 580:376-380), suggesting that these neurons can monitor ingestion using mechanosensory signals from the upper digestive tract. However, the precise origin of the signal during natural ingestion (i.e. in which digestive tract region, by which sensory neurons or mechanoreceptor molecules) still remains unclear. As a first step to answer these questions, we mechanically probed several subregions of each upper digestive tract organ in anesthetized mice and recorded the response of PB^{Pdyn} neurons using fiber photometry. Furthermore, to test the necessity of signals arising from each digestive tract organ, we transected the nerve branches innervating each digestive tract region. Collectively, our preliminary data suggest that PB^{Pdyn} neurons may monitor ingestion using signals generated from the esophagus and/or the adjacent digestive tract areas. While performing further experiments to pinpoint the region and the nerve responsible for the generation of signals related to PB^{Pdyn} neurons, we are also exploring the identity of mechanoreceptor cells and molecules underlying detection of ingestion.

Disclosures: **M. Kim:** None. **D. Koo:** None. **G. Han:** None. **H. Cho:** None. **D. Kim:** None. **G. Heo:** None. **S. Kim:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.03/JJ19

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant R01DK126740

Title: Adrenergic modulation of melanocortin pathway by hunger signals

Authors: *N. S. ATASOY[1], C. LAULE[1], I. AKLAN[1], H. KIM[1], Y. YAVUZ[2], T. ATES[1], D. ATASOY[1];
[1]Neurosci. and pharmacology, Univ. of Iowa, Iowa City, IA; [2]Yeditepe Univ., Istanbul, Turkey

Abstract: Norepinephrine (NE) is a well-known appetite regulator and several anti-obesity drugs target adrenergic system. To better understand the circuitry underlying adrenergic control of appetite, we investigated the paraventricular hypothalamus (PVN), a key brain region that integrates energy related signals and receives dense adrenergic input. We found that PVN NE level increases with signals of energy deficit and decreases with food access. This pattern is recapitulated by the activity of PVN innervating catecholaminergic axon terminals originating from NTS^{TH} (tyrosine hydroxylase) neurons. Optogenetic activation of rostral-NTS^{TH} to PVN projection elicited strong motivation to eat, comparable to 24 hours fasting, whereas its inhibition attenuated both fasting-induced & hypoglycemic feeding. We found that NTS^{TH}-axons functionally target PVN^{MC4R} neurons by predominantly inhibiting them, in part, through α1-adrenergic receptor mediated potentiation of GABA release from ARC^{AgRP} presynaptic terminals. Furthermore, glucoprivation suppressed PVN^{MC4R} activity, which was required for hypoglycemic feeding response. These results define an ascending NTS^{TH} to PVN^{MC4R} adrenergic circuit that conveys peripheral signals of energy deficit to the melanocortin pathway.

Disclosures: N.S. Atasoy: None. **C. Laule:** None. **I. Aklan:** None. **H. Kim:** None. **Y. Yavuz:** None. **T. Ates:** None. **D. Atasoy:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.04/Web Only

Topic: F.08. Food and Water Intake and Energy Balance

Support: MEXT/JSPS KAKENHI Grant 19K10039
MEXT/JSPS KAKENHI Grant 22K09900.

Title: Analysis of gaping reactions induced by emetine and cisplatin.

Authors: *M. FUNAHASHI, Z. WEI, H. HUANG, T. YOSHIZAWA, T. INUI;
Oral Physiol., Hokkaido Univ, Grad Sch. Dent. Med., Sapporo, Japan

Abstract: Emetine is an ingredient of the root of Carapichea Ipecacuanha, and its oral administration cause acute severe vomiting. Cisplatin is an antineoplastic drug that induces acute, late-onset and predictive nausea and vomiting. We previously reported emetine- and cisplatin-induced conditioned taste avoidance (CTA) to saccharin in rats. In the present study, we investigated gaping reactions induced by emetine and cisplatin to confirm if the emetine and cisplatin induce conditioned taste aversion. Gaping reactions were measured by using taste reactivity test (TR test) in male Sprague-Dawley rats (6-7 weeks old at the beginning of the experiment). Surgery was performed on rats to install an oral catheter under anesthesia with a combination anesthetic containing (mg/kg, i.p.): 0.15 medetomidine, 2 midazolam and 2.5 butorphanol. To analyze gaping reactions, the mouth movements of rats were recorded on video. We measured the number of gaping using offline video images. We performed TR test with administration of 0.1% saccharin (0.5ml/min, 8 min, p.o.) in rats that acquired CTA to saccharine by the conditioning with emetine (5.54 mg/kg, 1% BW, i.p.) and cisplatin (3 mg/kg, 1% BW, i.p.). The number of gaping reactions in rats conditioned with emetine and cisplatin was 58.0 ± 10.7 / 8 minutes (n = 5) and 123.67 ± 25.97 / 8 minutes (n = 6) ($p < 0.01$ in both groups). These results indicate the conditioned nausea produced by emetine- and cisplatin-induced CTA to saccharin, suggesting the aversive memory to sweetness produced by conditioning with emetine and cisplatin. These findings demonstrated that emetine and cisplatin induce conditioned nausea and that rats develop conditioned aversion to saccharin. The emetic effect of cisplatin is implicated to be greater than emetine.

Disclosures: M. Funahashi: None. **Z. Wei:** None. **H. Huang:** None. **T. Yoshizawa:** None. **T. Inui:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.05/JJ20

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant DK133818
NSF Grant IOS-1754878

Title: The role of diabetes insipidus in the fluid intake suppression hypersensitivity to central glucagon-like peptide-1 in the Brattleboro rat

Authors: *S. A. DAVID[1], D. J. BRAKEY[1], G. VARAVENKATARAMAN[1], M. J. PAUL[2], D. DANIELS[1,2,3];

[1]Biol. Sci., [2]Psychology, [3]Ctr. for Ingestive Behavior Res., State Univ. of New York, Univ. at Buffalo, Buffalo, NY

Abstract: Physiologically and behaviorally, fluid and food intakes are entangled. There is overlap in the brain regions that control the two types of ingestive behavior, and signaling peptides that affect one often affect the other. For example, glucagon-like peptide-1 (GLP-1) suppresses both food intake and fluid intake. The vasopressin-deficient Brattleboro rat has emerged as a potential model organism to separate fluid intake from food intake and could help isolate brain regions particularly involved in fluid intake control. Brattleboro rats drink copious amounts of water, but eat a similar amount of food when compared to wildtype rats. Moreover, Brattleboro rats are hypersensitive to the fluid intake suppression caused by central administration of a GLP-1 receptor (GLP-1R) agonist, Exendin-4 (Ex4), with no differences in sensitivity to the food intake effects. To evaluate if the hypersensitivity is directly related to the untreated diabetes insipidus (DI) in these rats, we implanted osmotic mini pumps containing desmopressin (ddAVP, a vasopressin type 2 receptor agonist). We found that alleviation of DI reduced the hypersensitivity, suggesting something transient and correctable is responsible for the hypersensitive response to Ex4. In an attempt to identify a brain region responsible for the exaggerated response to Ex4, we made direct injections of Ex4 into the tissue adjacent to the anteroventral third ventricle (AV3V) in wildtype and Brattleboro rats. There was a drug*genotype interaction on water intake after Ex4 when it was given in the AV3V at a dose that was ineffective at suppressing water when delivered to the 3V. This finding suggests that the anterior portions of the 3V are at least partly responsible for the hypersensitive response to Ex4 observed in Brattleboro rats. Together with previous work, these data provide useful context that will help identify specific brain areas that underlie different responses to GLP-1.

Disclosures: S.A. David: None. **D.J. Brakey:** None. **G. Varavenkataraman:** None. **M.J. Paul:** None. **D. Daniels:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.06/Web Only

Topic: F.08. Food and Water Intake and Energy Balance

Support: The Grants-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology in Japan (22K09900)

Title: Effects of conditioned taste aversion to saccharin on sweet food intake.

Authors: *Z. WEI, H. HUANG, T. YOSHIZAWA, T. INUI, M. FUNAHASHI; Hokkaido Univ., Sapporo, Hokkaido, Japan

Abstract: We examined whether rats avoid ingestion of saccharin-containing sweetened diet when they acquire conditioned taste aversion (CTA) to saccharin. The amount of saccharin

solution decreases in rats acquired CTA to saccahrin when they are reexposed to saccharin solution despite they feel thirst by 21 hours and 40 minutes water deprivation. In other words, the thirst-induced drinking behavior was suppressed by the taste aversive memory. Therefore, the present study was conducted based on the hypothesis that rats avoid intake of sweetened diet in defiance of hunger due to taste aversive memory. The male Sprague-Dawley rats (7 weeks old) were used as experimental animals, and we measured food and water intake, and body weight before and after the acquisition of CTA. The conditioned stimulus was 0.1% saccharin solution, and the unconditioned stimulus was nausea induction by injection of emetine hydrochloride (5.54 mg/kg, 1% BW, i.p.). Rats injected with saline (1% BW, i.p.) served as the control group. The sweetened diet was prepared by mixing powdered normal solid feed with an equal amount of 0.2% saccharin solution, forming it into the same shape as the solid feed, and drying it completely in a drying machine. Normal diet was made in the same way to ensure consistency in texture. After a one-day recovery day after CTA acquisition, the sweet diet test was conducted for five days, and the intake of sweet feed was significantly reduced on days 1-4 of the test compared to the intake of the normal diet on the conditioning day ($F(5,30) = 4.644$, $P < 0.01$, Dunnett's test). The control group did not show a significant decrease in sweet diet intake on any of the test days, but rather showed an increasing trend in intake on test days 3-5 compared to the conditioning days. These results indicate that the rats' feeding is suppressed by the taste aversion memory despite hunger. This suggests that the central mechanism of CTA may be implicated in the pathogenesis of eating disorders.

Disclosures: Z. Wei: None. **H. Huang:** None. **T. Yoshizawa:** None. **T. Inui:** None. **M. Funahashi:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.07/JJ21

Topic: F.08. Food and Water Intake and Energy Balance

Title: Trap2-dreadd mice for analyzing conditioned taste aversion: expression after lithium chloride and taste aversion after clozapine-n-oxide

Authors: J. M. COTE, *T. A. HOUPT;
Biol. Sci., Florida State Univ., Tallahassee, FL

Abstract: Static high magnetic fields (MFs) interact with the vestibular system of rodents. MFs cause perturbations such as head movements, circling, suppressed rearing, nystagmus, conditioned taste aversion and c-Fos in vestibular nuclei. While a useful correlate of neuronal activity, c-Fos expression alone is not informative of the functional contribution, if any, these active populations have in the behavioral effects of MF exposure. To prepare a model for elucidating the role of these active cells, we bred and validated TRAP2 mice expressing DREADDs in c-Fos-positive cells, which allows permanent genetic access to the cells activated

by the magnet. Because we plan to manipulate magnet-induced CTA by stimulating the DREADDs with the synthetic Clozapine-N-Oxide (CNO), we also determined whether CNO induced a CTA by itself. Targeted Recombination in Active Populations (TRAP2) mice (*Fos*$^{2A\text{-}iCreER}$ which express a tamoxifen-inducible Cre recombinase without disrupting endogenous c-Fos (Denardo et al. 2019) were bred with two floxxed effector lines expressing either excitatory (R26-hM3Dq/mCitrine) or inhibitory (R26-hM4Di/mCitrine) designer receptors exclusively activated by designer drugs (DREADD) generating *Fos*$^{2A\text{-}iCreER}$*-hM4Di and Fos*$^{2A\text{-}iCreER}$*-hM3Dq* mice. DREADD expression was induced by intraperitoneal injections of LiCl or NaCl (40ml/kg, 0.15M) paired with 4-hydroxytamoxifen (4-OHT; 50mg/kg) or sesame oil (5ml/kg) vehicle controls separated by one hour. DREADD expression was histologically verified by visualizing mCitrine with an anti-GFP antibody (Rockland Immunochemicals #600-101-215, 1:500) which was validated in transgenic hTh-GFP rats. Compared to uninduced vehicle controls, mice given LiCl paired with 4-OHT showed higher expression. However, there was noticeable baseline expression in uninduced controls, suggesting that a subtractive analysis will be required to control for transgene leakage. To assess the unconditioned effects of CNO in CTA wild-type male and female mice were placed on a water restriction schedule. On conditioning day, mice were given access to saccharin paired with CNO at 3 different doses: 0, 1, 3 and 10mg/kg (n=4/dose). CTA was assessed in 24-h, 2-bottle preference tests of saccharin vs water. Mice did not form a CTA at any dose of CNO, with all mice showing a high saccharin preference. This model can be used to selectively reactivate or inhibit cells activated by MF exposure, clarifying the role of these active cellular populations in MF behavioral effects.

Disclosures: J.M. Cote: None. **T.A. Houpt:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.08/Web Only

Topic: F.08. Food and Water Intake and Energy Balance

Support: FAPESP 2022/03615-5
FAPESP 2022/03616-1

Title: Food preference in different reproductive states in the experimental model of gestational diabetes

Authors: K. M. GODEGUEZI, M. S. AGOSTINI, M. G. MARTINS, ***A. C. I. KISS**; UNESP Botucatu, Botucatu, Brazil

Abstract: Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy. It is known that inadequate nutrition can worsen GDM and that food preference is an important aspect to guide food intake. The nutrition of pregnant women has an impact on the glycemic homeostasis and is an important tool in the treatment of pregnant women with GDM.

The study of different aspects of maternal food preference can contribute to a better understanding of food choices and can also serve as a basis for clinical studies that can improve nutritional counseling for women with GDM. Therefore, the aim of the present study was to evaluate the food preference of rats in different reproductive states in the experimental model of gestational diabetes. To achieve this goal, an experimental model of mild hyperglycemia induced by the administration of streptozocin (STZ) during pregnancy was used. Part of the rats received i.p. injection of STZ diluted in citrate buffer on day 7 of pregnancy (STZ, n=11), while the other females received only buffer (Control, n=9). The food preference test was conducted at 4 different times: before mating, during pregnancy, during lactation, and post-lactation. The test consisted of offering 3 types of special diets (high sugar, high fat, and high protein) for a period of 12 hours and later calculating the food preference index for each diet. As expected, food preference was modified according to the reproductive state. Overall, there was a reduction in the preference for the high fat and high protein diet and an increase in the preference for the high sugar diet over time. Maternal hyperglycemia reduced the preference for high protein diet during lactation, but there was no significant interaction between maternal metabolism and reproductive state for none of the diets. In conclusion, food preference changed according to the reproductive state and maternal diabetes contributed to a reduced high protein diet preference during lactation.

Disclosures: K.M. Godeguezi: None. **M.S. Agostini:** None. **M.G. Martins:** None. **A.C.I. Kiss:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.09/JJ22

Topic: F.08. Food and Water Intake and Energy Balance

Support: National Health and Medical Research Council Grant
Australian Government Research Training Program Scholarship

Title: The role of AgRP neurons in the regulation of feeding following vertical sleeve gastrectomy

Authors: *C. R. TEDESCO, C. S. MITCHELL, I. SUCQUART, D. P. BEGG;
Sch. of Psychology, Univ. of New South Wales, Randwick, Sydney, Australia

Abstract: The prevalence of obesity has risen dramatically in recent decades, representing a serious public health concern. Currently, bariatric surgeries such as the vertical sleeve gastrectomy (VSG) are the most effective long-term treatment for obesity. The efficacy of VSG is primarily mediated through a reduction in food intake. Although the VSG procedure involves removing the greater curvature of the stomach, evidence suggests that reduced feeding after surgery is *not* due to any kind of physical restriction on the amount of food that can be consumed. Instead, VSG potentially causes alterations in neuronal pathways involved in the

regulation of feeding. We investigated whether VSG was associated with changes in the regulation of food intake by Agouti-Related Peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus (ARC). To address this question, we used male transgenic AgRP-Cre C57BL/6 mice that were maintained on a high-fat diet for 8-12 weeks prior to VSG (n = 7) or sham (n = 7) surgery. First, we selectively expressed excitatory designer hM3D(Gq) receptors in ARC AgRP neurons of VSG and sham mice via bilateral injection of a DIO-hM3D(Gq) virus into the ARC. Activation of these neurons via administration of clozapine-N-oxide (1 mg/kg; i.p.) increased consumption of various diets (including standard rodent chow, high-fat chow, sucrose solution, and a lipid emulsion) relative to a vehicle injection across counterbalanced test days. Further, stimulating ARC AgRP neurons increased feeding to the same degree in both VSG and sham animals. This lack of difference in food consumption between VSG and sham groups demonstrates that VSG does not physically restrict feeding, and suggests that VSG does not alter how ARC AgRP neurons respond to chemogenetic stimulation. To examine whether VSG alters the basal activity of these neurons in response to feeding, we next conducted in vivo fibre photometry experiments to monitor bulk calcium signalling as a proxy for neuronal activity. In a separate cohort of VSG (n = 7) and sham (n = 6) mice, we selectively expressed the calcium indicator GCaMP6s in ARC AgRP neurons and implanted a fibre optic cannula above the ARC. Animals were food-deprived overnight and presented with a pellet of high-fat chow after a baseline recording window. Analysis of calcium signals pre- and post-consumption indicated greater suppression of bulk ARC AgRP neuronal activity upon feeding in VSG compared with sham mice. Together, our findings demonstrate that VSG does not disrupt AgRP-mediated feeding, and indicate that VSG may restore the functioning of ARC AgRP neuronal activity in response to feeding.

Disclosures: C.R. Tedesco: None. **C.S. Mitchell:** None. **I. Sucquart:** None. **D.P. Begg:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

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Program #/Poster #: PSTR286.10/JJ23

Topic: F.08. Food and Water Intake and Energy Balance

Support: Boehringer Ingelheim Fonds PhD Fellowship
NIH grant R01MH06364917
Alzheimer's Association Research Grant AARG-21-850571
Whitehall Foundation Research Grant 2018- 08-88

Title: Mnemonic and metabolic interactions across the hippocampal-hypothalamic circuit

Authors: *E. KAYA[1], E. WEGIENKA[3], A. AKHTARZANDI-DAS[3], A. EBAN-ROTHSCHILD[2], G. ROTHSCHILD[4];
[2]Univ. of Michigan, Ann Arbor, [1]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [4]Univ. of Michigan, [3]Univ. of Michigan, Ann Arbor, MI

Abstract: For all organisms from bacteria to humans, life is a journey in search of resources to keep the internal environment in a desirable state. To find these resources, organisms perform stimulus-seeking behaviors during which actions resulting in improved bodily states are repeated while others are not. While even bacteria exhibit such coordination of behaviors informed via consequences of earlier actions, the evolution of the nervous system has allowed more complex organisms to use more sophisticated strategies to learn from the past, anticipate the future, and respond quickly for effective metabolic regulation. In mammals specifically, the hippocampus matches internal signals to actions to form memories and guide future behavior. To date, numerous studies have shown that hippocampal-cortical communication during a hippocampal oscillatory event called sharp wave ripples (SWR) is critical for memory processes. However, SWRs can also propagate to subcortical structures that are involved in metabolic regulation, which implies a potential dual role of SWRs in memory and metabolism. Indeed, a recent study showed that SWRs can modulate peripheral glucose metabolism. Yet, we still lack a comprehensive understanding of the metabolic functions of SWRs and downstream pathways that communicate SWRs to the body. To address these gaps, we tested the effects of feeding and metabolic hormones on SWRs in freely behaving and naturally sleeping mice. Our results show that SWRs during sleep are modulated by recent food intake and by metabolic hormones in a dose-dependent manner. To determine whether feeding-modulated hippocampal SWRs influence downstream subcortical structures involved in feeding regulation, We combined electrophysiological recordings in the hippocampus and optical recordings in the lateral hypothalamus via fiber photometry. We found that lateral hypothalamic GABAergic and Glutamatergic populations exhibit a robust and consistent increase in activity that peaks ∼300 ms after SWRs. Together, we identify the modulation of SWRs by metabolic signals, and offer hippocampal-lateral hypothalamic communication around SWRs as a potential mechanism by which SWRs can modulate peripheral physiology and behaviors.

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Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

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Program #/Poster #: PSTR286.11/JJ24

Topic: F.08. Food and Water Intake and Energy Balance

Support: CREST grant, JPMJCR21P1
A-STEP grant, JPMJTR20UT
AMED grant, JP 21lm0203014

Title: Dietary GABA enhances the postprandial activation of vagal afferents to promote satiation

Authors: *Y. IWASAKI[1], U. NAKAMURA[2], T. NOHMI[1], R. SAGANE[2], M. KIM[2], K. OHBAYASHI[1];
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Abstract: [Background] Gamma-aminobutyric acid (GABA) is known as the main inhibitory neurotransmitter, and it is also present in foods. Recently, GABA has become widely available as a dietary supplement with beneficial effects on brain functions, such as reducing stress and enhancing sleep. However, it has long been believed that GABA is unable to cross the blood-brain barrier. Therefore, it remains unclear how dietary GABA affects the brain. [Aim] In this study, we aimed to investigate the effects of single peroral (po) administration of GABA on feeding behavior, a brain function, and determine the involvement of vagal afferents. [Methods] We measured the food intake after a single GABA administration via oral gavage in C57BL/6J mice. We investigated whether a single po GABA administration could increase the expression of phosphorylated ERK1/2 (pERK1/2), serving as cellular/neuronal activity markers, in vagal afferent nodose ganglion neurons. [Results] Po GABA immediately before refeeding transiently reduced food intake in overnight fasted mice without causing aversion. This effect was blunted by surgical and chemical denervation of vagal afferents. However, po GABA alone did not alter the expression of pERK1/2 in vagal afferent nodose ganglion neurons, and po GABA 30 min before refeeding did not alter feeding. These findings suggested that GABA interacts with factors triggered by meals and regulates feeding. Simultaneously po administration of GABA and liquid diet (Ensure H) potentiated the postprandial activation of vagal afferents and robustly enhanced meal-evoked satiation. [Conclusions] The findings of this study indicate that dietary GABA enhances the activation of postprandial vagal afferents, potentially through interaction with meal-evoked factors, leading to the regulation of brain functions such as feeding behavior.

Disclosures: Y. Iwasaki: 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.; Pharma Foods International Co., Ltd. **U. Nakamura:** A. Employment/Salary (full or part-time):; Pharma Foods International Co., Ltd.. **T. Nohmi:** None. **R. Sagane:** A. Employment/Salary (full or part-time):; Pharma Foods International Co., Ltd. **M. Kim:** A. Employment/Salary (full or part-time):; Pharma Foods International Co., Ltd.. **K. Ohbayashi:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.12/JJ25

Topic: F.08. Food and Water Intake and Energy Balance

Title: Ghrelin-responsive mediobasal hypothalamic neurons mediate exercise-associated food intake and exercise endurance

Authors: *O. SINGH[1], S. B. OGDEN[1], S. VARSHNEY[1], K. SHANKAR[1], D. GUPTA[1], S. PAUL[1], S. OSBORNE-LAWRENCE[1], C. P. RICHARD[1], N. P. METZGER[1], C. LAWRENCE[1], L. LEON MERCADO[1], J. M. ZIGMAN[1,2];
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Abstract: The orexigenic hormone ghrelin doubles during high-intensity interval exercise (HIIE). Without the action of this increased ghrelin (as in mice lacking the ghrelin receptor, GHSR), exercise reduces food intake. Further, GHSR-null mice exhibit diminished exercise endurance. These data suggest that ghrelin limits the capacity of exercise to restrict food intake but enhances endurance. In this study, we aimed to determine whether GHSR-expressing neurons in the mediobasal hypothalamus (MBH) mediate the effects of exercise on food intake and regulate exercise endurance. We stereotaxically delivered the inhibitory DREADD virus AAV2-hSyn-DIO-hM4D(Gi)-mCherry to the MBH of GHSR-IRES-Cre mice. CNO was administered to chemogenetically inhibit the activity of GHSR-expressing neurons infected with the inhibitory DREADD virus. Mice were subjected to HIIE and exercise endurance protocols, and we assessed food intake and MBH c-fos induction in response to administered ghrelin. We used histochemistry to classify mice as correctly targeted ("hits," n=16) or incorrectly targeted ("misses," n=11). Also, we evaluated the impact of the DREADD virus on the activity of GHSR-expressing MBH neurons by performing immunohistochemistry for c-fos following exercise endurance. DREADD-assisted inhibition of GHSR-expressing MBH neuronal activity suppressed food intake by 33.8% following HIIE, as well as maximal running distance (by 20.7%), total running duration (by 14.5%), and maximum running speed (by 14.5%) during the exercise endurance protocol (compared to "hits" treated with saline). Moreover, DREADD-assisted inhibition of GHSR-expressing MBH neuronal activity increased blood glucose levels by 18.4% and blood lactate levels by 24.6% following the exercise endurance protocol (compared to "hits" treated with saline). "Hits" treated with CNO also exhibited a 57.2% reduction in food intake and a 71.4% reduction in c-fos induction within the arcuate nucleus (ARC) in response to ghrelin administration, compared to "misses" treated with CNO. We also observed reductions in numbers of c-fos-positive cells in the ARC (by 20.3%) and ventromedial hypothalamus (by 22.4%) in the hM4Di-injected "hits" compared to control mCherry virus-injected "hits" after CNO + endurance exercise. All listed %'s are significant (P-values<0.05). Thus, activation of ghrelin-responsive MBH neurons is necessary for the normal feeding response to HIIE, the typical endurance exhibited by mice during a forced exercise endurance protocol, food intake and MBH neuronal activation in response to administered ghrelin, and the usual blood glucose and lactate responses to prolonged exercise.

Disclosures: O. Singh: None. **S.B. Ogden:** None. **S. Varshney:** None. **K. Shankar:** None. **D. Gupta:** None. **S. Paul:** None. **S. Osborne-Lawrence:** None. **C.P. Richard:** None. **N.P. Metzger:** None. **C. Lawrence:** None. **L. Leon Mercado:** None. **J.M. Zigman:** A. Employment/Salary (full or part-time):; UT Southwestern Medical Center. 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.; This work was supported by P01 DK119130-01 to JMZ.. Other; JMZ consulted for Helsinn Healthcare S.A. and Dexcel Pharma Technologies Ltd.

when these studies were performed and receives research funding from Novo Nordisk for another project..

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.13/KK1

Topic: F.08. Food and Water Intake and Energy Balance

Support: Fapesp 2022/09687-8
Fapesp 2019/20602-1
FAEPA

Title: Pde4 inhibitor acts in the brain to ameliorate obesity-induced neuroinflammation

Authors: *H. DA SILVA[1], L. DUARTE[1], M. SEIXAS[2], J. ANTUNES-RODRIGUES[2], F. DE PAULA[3], L. ELIAS[2];
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Abstract: Obesity is associated with peripheral and central low-grade inflammation characterized by increased pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF). Phosphodiesterase 4 (PDE4) modulates inflammatory responses and its inhibitor can strongly reduce TNF release and inflammation. Additionally, PDE4 knockout mice were shown to be resistant to diet-induced obesity (DIO). The aim of this study was to investigate the role of central and peripheral effects of PDE4 in DIO. To attain this purpose, mice were treated with rolipram, a PDE4 inhibitor capable of crossing the blood-brain barrier, or YM-976, a brain-impermeable inhibitor. All experimental protocols were approved by the Ethics Committee for Animal Use of the Ribeirao Preto Medical School. Male C57Bl6 mice were fed with either chow or a high-fat diet (HFD; 60% fat) for 10 weeks and in the 8th week, they received daily subcutaneous injections of vehicle (VEH), rolipram (2mg/kg) or YM-976 (2mg/kg). During the experimental period, food intake and body weight were monitored and at the end of the study, inguinal, retroperitoneal, and brown fat pads were collected for analysis. Rolipram decreased the absolute value and change of body weight in the HFD group, which was associated with a decrease in epididymal and retroperitoneal fat pad weight, with no effect in the chow group. Remarkably, rolipram was able to decrease energy intake and energy efficiency, as well as to increase energy expenditure in HFD-treated animals. In addition, PDE4 inhibition decreased NF-KB translocation to the nucleus in the hypothalamus of HFD-treated animals, which is consistent with a reduction in neuroinflammation. In contrast to rolipram, the YM-976 inhibitor was unable to ameliorate the metabolic changes in DIO. These results indicated that the beneficial metabolic effects of PDE4 inhibitors on DIO occur through attenuation of central inflammation and reinforce PDE4 as a potential target for the treatment of obesity. Financial support: FAPESP, CNPq, FAEPA

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Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.14/KK2

Topic: F.08. Food and Water Intake and Energy Balance

Support: HRC project grant

Title: Insensitivity to the feeding response of exogenous ghrelin develops during pregnancy

Authors: *C. L. MURRELL[1], Z. B. ANDREWS[2], D. R. GRATTAN[1,3], S. L. LADYMAN[1,3]; [1]Univ. of Otago, Dunedin, New Zealand; [2]Dept. of Physiol., Monash Biomedicine Discovery Institute, Monash Univ., Clayton, Victoria, Australia; [3]Maurice Wilkins Ctr. for Mol. Biodiscovery, Auckland, New Zealand

Abstract: During pregnancy and lactation, the maternal body undergoes many metabolic adaptations, including increased food intake, to support the energy demands of the growing fetus and provide nutrition through milk production after birth. Ghrelin, an orexigenic hormone, activates agouti-related peptide (AgRP) neurons in the arcuate nucleus promoting rapid food intake. Here, we investigate the contribution of ghrelin in elevated maternal food intake. To determine whether increased sensitivity to ghrelin contributes to maternal hyperphagia, female C57/B6 mice were injected (i.p.) with either ghrelin (0.3mg/kg) or vehicle (saline) at four physiological timepoints: prior to pregnancy (virgin), day 8 (P8) and 15 of pregnancy (P15) and lactational day 10 (L10) then 2h food intake was measured. In virgin mice, ghrelin treatment (n = 16) acutely increased food intake compared to the saline-treated group (n = 16). Interestingly, during pregnancy (both P8 and P15) there was no difference in food intake between ghrelin and saline treatment groups (2-way ANOVA, interaction treatment x physiological state $p = 0.0482$, n = 8-18) suggesting a lack of sensitivity to the ghrelin-induced feeding response. By day 10 of lactation the food intake stimulating effect of ghrelin was restored (Mann-Whitney $p = 0.0223$, n = 10-12). *In vivo* GCaMP fibre photometry of the AgRP neuron population was used to assess if an attenuated response to ghrelin by AgRP neurons underlies the lack of ghrelin-induced food intake in pregnancy. Recordings of AgRP neuron population activity in response to ghrelin (0.3mg/kg i.p.) were collected from virgin, pregnant and lactating mice. At all timepoints, ghrelin treatment resulted in a well-established increase in AgRP neuron activity (n = 7 per time point). In a final experiment, female (groups of virgin, P15 and L10 n = 9-10) AgRP cre x Td-tomato mice were treated with either ghrelin (0.3mg/kg i.p.) or saline then perfused with 4% paraformaldehyde and brains were processed for c-fos immunofluorescent labelling. Ghrelin-treatment significantly increased c-fos expression in AgRP neurons, even in pregnancy (2-way ANOVA, effect of treatment $p = <0.0001$). Overall these results indicate that increased ghrelin sensitivity does not contribute to increased maternal food intake. In contrast to this hypothesis, a

temporary insensitivity to the ghrelin-induced feeding response develops during pregnancy, and this is not associated with a change in acute response of AgRP neurons to ghrelin. Therefore, it seems likely that this change in behavioural response to ghrelin develops downstream of AgRP neurons.

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Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.15/KK3

Topic: F.08. Food and Water Intake and Energy Balance

Support: National Research Foundation of Korea Grant

Title: Sirtuin1-induced deacetylation of TTF-1 is important in hypothalamic control of energy homeostasis

Authors: *D. KANG, B. LEE;
Univ. of Ulsan, Ulsan, Korea, Republic of

Abstract: When an animal is starving, thyroid transcription factor-1 (TTF-1) stimulates appetite by regulating the expression of agouti-related peptide (AgRP) and proopiomelanocortin (POMC) genes in the hypothalamus. However, the mechanism by which TTF-1 responds to a decrease in the body's energy level is not known. In this study, we present evidence that the NAD^+-dependent deacetylase Sirtuin 1 (Sirt1) plays a crucial role in mediating the actions of TTF-1 in response to energy deficiency. We discovered that energy deficiency enhances the expression of both Sirt1 and TTF-1, leading to the deacetylation of TTF-1 through increased interaction between TTF and Sirt1. Both energy deficiency-induced and resveratrol-induced activation of Sirt-1 resulted in an increase in the nuclear translocation of TTF-1. However, this effect was inhibited by treatment with a Sirt1 inhibitor. Notably, the action of TTF-1 on AgRP and POMC gene expression was hindered due to the inability of TTF-1 to undergo deacetylation, which was induced by a point mutation in a lysine residue of TTF-1. In summary, these findings indicate that energy deficiency-induced deacetylation of TTF-1 plays a crucial role in the overall regulation of whole-body energy homeostasis by TTF-1, particularly through the regulation of AgRP and POMC gene expression.

Disclosures: D. Kang: None. **B. Lee:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.16/KK4

Topic: F.08. Food and Water Intake and Energy Balance

Support: CNPq
PROPE UNESP
FAPESP

Title: Participation of P2 purinergic receptors in pilocarpine-induced water intake

Authors: *P. M. DE PAULA, P. A. A. GOIS, J. V. MENANI;
Physiol. and Pathology, Sao Paulo State Univ., UNESP Araraquara, Brazil

Abstract: Intraperitoneal (ip) injection of pilocarpine (PILO, muscarinic cholinergic agonist) induces salivation, water intake and changes in body temperature. These effects are due to a direct action on the salivary glands and central nervous system (CNS). ATP (adenosine 5-triphosphate) is a neurotransmitter in the peripheral and CNS and is responsible for activating P2 purinergic receptors located in various regions including the salivary glands. Preliminary results from our laboratory showed that ATP injected intraperitoneally (ip) reduced PILO-induced salivation, suggesting the participation of peripheral P2 purinergic receptors in salivary secretion. The aim of the present study was to investigate the effects of ip injection of ATP (a natural agonist of P2 purinergic receptors) on water intake and changes in body temperature induced by PILO also administrated ip. Male Holtzman rats (300-350 g, n=18) were used. The experimental protocols were approved by Ethical Committee for Animal Care and Use - CEUA from Dentistry School of Araraquara, UNESP (Proc. CEUA number 11/2019). A group of 10 rats received ip injection of PILO (1 mg/kg of body weight) to induced water intake. Ten minutes before, half of the group received an ip injection of ATP (200 mg/kg of body weight) and the other half received saline. Then water was offered in graduated burettes fitted with metal drinking spouts. The results showed that ip injections of ATP reduced PILO-induced water intake (0.2 +/- 0.1 mL/15 min, vs. saline + PILO: 2.2 +/- 0.6 mL/15 min, $p<0.05$). Another group of 8 rats was submitted to a median laparotomy for the placement of body temperature sensors in the abdominal cavity. The results showed that ip injection of PILO did not alter body temperature (0.3 +/- 0.1 °C, vs. saline: 0.3 +/- 0.1 °C) and the combination of ATP + PILO also did not change body temperature (0.2 +/- 0.1 °C). Thus, the results suggest that ip injection of ATP reduced PILO-induced water intake, but PILO alone or combined with ATP did not change body temperature in rats.

Disclosures: P.M. De Paula: None. **P.A.A. Gois:** None. **J.V. Menani:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.17/KK5

Topic: F.08. Food and Water Intake and Energy Balance

Support: PO1 DK08876
RO1 DK118725

Title: Stimulation of sensory or motor vagal neurons produces opposite effects on glucose homeostasis

Authors: *L. A. LEON-MERCADO[1], S. DEJA[2], A. TINAJERO[1], B. CHEN[1], J. LEE[1], S. LEE[1], S. BURGESS[2], J. ELMQUIST[1];
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Abstract: The parasympathetic nervous system contributes to the regulation of food intake, body weight and glycemia. In recent years, parasympathetic stimulation via the vagus nerve has emerged as a potential therapy to treat obesity and metabolic diseases. However, reports from different studies have shown dissimilar results, due by the complex mixture of sensory and motor fibers comprising the vagus nerve. To better characterize the mechanisms controlling the glycemic response to vagal stimulation, we decided to genetically target the sensory or motor vagal pathways individually. Using optogenetic techniques combined with transgenic mouse models, we stimulated the vagal sensory terminals in Nav1.8- Cre mice, parasympathetic motor neurons in Chat-Cre mice or both in Phox2b-Cre mice at the level of the brainstem. In addition, we performed optogenetic stimulation and various metabolic tests to evaluate hepatic glucose metabolism, glucose tolerance and insulin sensitivity in awake, freely moving mice. We found that stimulation of the sensory afferents in the NTS of Nav1.8-expressing neurons produced hyperglycemia accompanied by glucose intolerance and insulin insensitivity. On the other hand, optogenetic stimulation of the vagal motor Chat-expressing neurons increased both glucose tolerance and insulin sensitivity. Intriguingly, optogenetic stimulation of the dorsal vagal complex of Phox2b-Cre mice activated both sensory and motor vagal branches and produced hyperglycemia. Suggesting a predominant role of the vagal sensory input in the control of glycemia. Our results provide further insight into the complexity of vagal control of glucose metabolism by sensory and motor neurons. Moreover, vagal stimulation could be fine-tuned to address acute glucose fluctuations of hyper and hypoglycemia, both factors associated to diabetes.

Disclosures: L.A. Leon-Mercado: None. **S. Deja:** None. **A. Tinajero:** None. **B. Chen:** None. **J. Lee:** None. **S. Lee:** None. **S. Burgess:** None. **J. Elmquist:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.18/KK6

Topic: F.08. Food and Water Intake and Energy Balance

Support: Poncin Foundation Pre-doctoral Fellowship

Title: Characterization of nucleus of the solitary tract (NTS) neurons with direct inputs to the ventral tegmental area.

Authors: *C. R. RITCHEY, D. J. ROSSI, J. H. PETERS;
Integrated Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Goal-oriented behaviors, including food intake, are driven by evolutionarily ancient and extensive neurocircuitry that integrates internal and external cues. The midbrain ventral tegmental area (VTA) shapes these behaviors via dense dopaminergic projections to many key forebrain areas. In addition, the VTA serves as an integrator of neural inputs from throughout the brain that modulate VTA output to produce broad, state-dependent, changes that reflect the balance of internal and external considerations. While descending cortical and limbic inputs to the VTA are well characterized, the origins and mechanisms of hindbrain inputs to the VTA remain largely unknown. The brainstem nucleus of the solitary tract (NTS) is the primary site for integration of viscerosensory and taste information conveyed through the cranial nerves and is essential for the control of food intake. Importantly, the NTS has been shown to form direct connections with the VTA, but little is known about the anatomical and neurophysiological nature of these projecting neurons, or how they shape VTA output to influence appetitive feeding behaviors. The purpose of this study was to characterize the anatomical and neurophysiological properties of NTS neurons with direct projections to the VTA. Using VTA-targeted retrobead injections, we found that a subpopulation of NTS neurons form direct monosynaptic connections with the VTA that are distributed through all rostro to caudal levels of the NTS; with greater prevalence in the medial and caudal NTS. Further, immunohistochemical analysis for tyrosine hydroxylase demonstrated that a significant population of these VTA-projecting NTS neurons are catecholaminergic. Using patch-clamp electrophysiology, we assayed the relative prominence of glutamatergic and GABAergic synaptic contacts, connectivity to the solitary tract, and responsiveness to feeding peptides. We found that VTA-projecting NTS neurons respond to the peptides cholecystokinin and exendin-4 and receive predominately polysynaptic innervation by the solitary tract. These findings are the first step in characterizing the nature of NTS inputs to the VTA that may play a role in regulating the mesolimbic dopaminergic pathway to control appetitive feeding responses.

Disclosures: **C.R. Ritchey:** None. **D.J. Rossi:** None. **J.H. Peters:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.19/KK7

Topic: F.08. Food and Water Intake and Energy Balance

Support: Fapesp
Cnpq
Faepa

Title: Pi3k in the ventromedial hypothalamus mediates estradiol actions in the regulation of energy homeostasis

Authors: A. DE JESUS[1], R. DOS-SANTOS[1], I. RODRIGUES-SANTOS[1], H. DA SILVA[2], M. MANTOVANI-MATA[3], R. VOLPI[3], G. GONÇALVES[2], L. NAVEGANTES[4], C. F. ELIAS[6], J. ANTUNES-RODRIGUES[7], ***L. ELIAS**[5];
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Abstract: Decreased production of 17β-estradiol (E2) after menopause is associated with an increased risk of developing obesity and type 2 diabetes mellitus. In experimental animals, decreased circulating levels of E2 induced by ovariectomy leads to the development of hyperphagia and, obesity, which are reverted by hormone replacement. Ventromedial hypothalamus (VMH) has been considered one of the main regions of ovarian hormone action in the regulation of energy homeostasis. However, the intracellular mechanisms involved in E2 actions in the VMH to control body weight are still poorly understood. The aim of this study was to investigate the role of phosphoinositide 3-kinase (PI3K) signaling in VMH neurons that express the steroidogenic factor 1 (SF1) in ovariectomized females treated with E2. To assess the role of the PI3K signaling we used cre-lox technology to generate female mice with specific disruption of P110α catalytic subunit in SF1 neurons. All experimental protocols were approved by the Ethics Committee for Animal Use of the Ribeirao Preto Medical School. Food intake, body weight and energy expenditure were monitored and at the end of the study, inguinal, retroperitoneal, and brown fat pads were collected. Deletion of P110α catalytic subunit in SF1 neurons of VMH partially reduced the effects of E2 in OVX females on body weight gain. In addition, indirect calorimetry demonstrated that energy expenditure was increased in P110αflox/flox OVX mice that received E2 treatment, compared with respective vehicle group. However, E2 treatment did not increase energy expenditure in SF-1cre;P110αflox/flox mice . In addition, in this group there was a reduction of E2 effect to increase thermogenesis in the brown adipose tissue (BAT) which was associated with a decrease in sympathetic activity in this tissue . These results indicated that PI3K pathway in SF1 neurons is required to the estradiol effects on the energy homeostasis.

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Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.20/KK8

Topic: F.08. Food and Water Intake and Energy Balance

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Title: Representation of bodily signals in the lateral parabrachial nucleus during natural feeding

Authors: *H. J. CHOH[1], R. A. ESSNER[1,2], K. RUDA[1], M. L. ANDERMANN[1,2];
[1]Beth Israel Deaconess Med. Ctr., Boston, MA; [2]Program in Neurosci., Harvard Med. Sch., Boston, MA

Abstract: Interoception, the sensing of internal states, is vital for maintaining physiological homeostasis. For example, the proper regulation of food intake requires animals to perceive satiety signals related to stretch and/or nutrients within the gastrointestinal tract. These visceral signals are relayed to the brain via vagal, spinal, and hormonal pathways, which converge in the brainstem lateral parabrachial nucleus (LPBN) to drive associated changes in behavior and physiology through forebrain projections. Previous work has identified subpopulations of LPBN neurons based on gene expression, such as calcitonin gene-related peptide (CGRP)-expressing neurons in the LPBN that suppress appetite and process threat signals. Whether these subpopulations have dedicated functions or not is still unclear, preventing a comprehensive understanding of how the LPBN contributes to interoception during behaviors such as ingestion. In addition, several forebrain regions send feedback to LPBN, providing a basis to affect LPBN activity and associated feeding behaviors. For example, the insular cortex (InsCtx), which makes predictions about future energy states during feeding, sends a large feedback projection to LPBN. Thus, InsCtx may alter how LPBN processes interoceptive information. To understand how LPBN integrates autonomic signals and top-down modulation across physiological states, we recorded from CGRP neurons in LPBN using in vivo fiber photometry of bulk calcium signals. As expected, we found that CGRP neurons respond to liquid food (Ensure) consumption, mild tail shocks, and visceral malaise. We are also exploring the modulation of this activity by InsCtx inputs. Our preliminary data show that brief stimulation of InsCtx-LPBN axons drives robust responses in CGRP neurons, suggesting that InsCtx influences interoceptive processing in LPBN. To parse the sensory preferences of all LPBN neurons regardless of genetic subtype, we have further developed a novel method of chronic two-photon calcium imaging in awake mice during various visceral stimuli. Our data reveal a wave-like pattern of activation during ingestion of Ensure, which we hypothesize is indicative of a viscerotopic map of the gastrointestinal tract. These experiments reveal functional organization and diversity of representations of bodily signals in LPBN.

Disclosures: H.J. Choh: None. **R.A. Essner:** None. **K. Ruda:** None. **M.L. Andermann:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.21/KK9

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH NIDA R01 DA025634

Title: Nociceptin Receptor Antagonism Modulates Dopamine Responses to Water in Thirsty Rats

Authors: *P. BAZZINO, M. LOH, M. ROITMAN;
Univ. of Illinois at Chicago, Chicago, IL

Abstract: Thirst, a powerful drive for fluid consumption to restore balance, recruits dopamine responses to water and water-predictive cues. We measured the activity of ventral tegmental area (VTA) dopamine neurons with fiber photometry during intra-oral infusions of water. In thirsty rats, dopamine responses are initially high but as the session proceeds and animals become satiated (400 microliters over 10 seconds per trial; 50 trials; 30-60s variable intertrial interval), dopamine responses diminish (slope of regression line: -0.03 z-score/trial), especially as rats begin to reject the intra-oral infusions. The mechanisms by which dopamine responses are modulated during thirst satiation remain unknown. Recent work (Parker et al. 2019) supports a role for nociceptin peptide and receptors within the paranigral VTA in limiting food reward-directed behavior during operant responding. Intra-oral delivery of fluids represents an ideal foundation to further examine a role for nociceptin in negative regulation of reward. This method provides an optimal platform for studying the ingestion or rejection of taste stimuli. Here, cre-dependent GCaMP6 and a fiber optic was targeted to the VTA of TH-cre+ rats. Following recovery, thirsty rats were pre-treated (t-15min) with different doses of the nociceptin antagonist J-113397 (0, 2.5, 5, or10mg/kg, i.p. treatment order counterbalanced across rats) and intra-oral infusions of water were made. Three days were inserted between treatment days. Interestingly, when administering 5mg/kg of nociception antagonist, there was a more shallow slope for dopamine across trials and this was correlated with increase in trials prior to rejection. These findings suggest that nociceptin signaling may contribute to the satiation of multiple motivational drives including thirst.

Disclosures: P. Bazzino: None. **M. Loh:** None. **M. Roitman:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.22/KK10

Topic: F.08. Food and Water Intake and Energy Balance

Title: An Open-Source Licking Box for Precise Measurement of Liquid Intake and Licking Microstructure

Authors: *A. KANAKAM, M. OLVERA-CALTZONTZIN, S. BRESLIN, D. MEYER, S. A. STERN;
Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: Title: “AnOpen-Source Licking Box for Precise Measurement of Liquid Intake and LickingMicrostructure”Liquidintake has proven invaluable in the exploration of various fundamental biologicalquestions, ranging from motivation and drug addiction to anhedonia, feeding behaviors,memory, and learning. However, researchers face a significant challenge in accuratelymeasuring liquidintake, as most existing methods fail to account for the intricate lickingmicrostructure. This oversight results in the loss of important information and an increasedmargin of human error. Additionally, commercially available options for measuring liquidintakeoften come with exorbitant prices,lack customization options, and possessrigid analysiscapabilities.To address these limitations, we have developedand validated an innovative,open-source, printable, and low-cost Arduino based licking box system. Each box contains twoliquid taps which are linked with anArduinosystem, which cankeeptrack of 10tapssimultaneously, thus allowing for the testing of upto5mice inasingle recording. This Arduinosystem is paired with auser-friendly interface which cananalyze the dataover acumulative,differential, and groupcomparisonformat. Tovalidate the functionality of our licking box weconducted astandard two-bottle conditioned taste aversiontask. During the habituationperiod,mice were allowed toacclimate tothe experimental setup, which had initially only containedwater inboth taps. Subsequently, the mice were introduced tothe same setup, but with sucroseinone of the taps. Following this session, mice were injected with lithium chloride toinducevisceral malaise or saline as acontrol. We thenconducted atest sessiontoexamine successfulaversionmemory tothe sucrose tap. We were able todemonstrate that the licking boxesaccurately kept track of licking events across all taps, allowing for reliable quantificationinthesubsequent dataanalysis. This novel experiment system has anumber of advantages, with itbeing much more precise thansome existing methods of quantifying intakes, such asmeasuring the volume of intake or manually observing licking events. By offering an accessibleand affordable solution, our novel licking system fills a crucial gapin the field of liquidintakemeasurement.

Disclosures: A. Kanakam: None. **M. Olvera-Caltzontzin:** None. **S. Breslin:** None. **D. Meyer:** None. **S.A. Stern:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.23/KK12

Topic: F.08. Food and Water Intake and Energy Balance

Support: University of Iowa startup funds (JCG)

Title: Sodium appetite and thirst do not require angiotensinogen production in astrocytes or hepatocytes

Authors: *L. PELTEKIAN[1], S. GASPARINI[1], F. S. FAZAN[1], S. KARTHIK[1], G. IVERSON[1], J. M. RESCH[2], J. C. GEERLING[1];
[1]Neurol., [2]Univ. of Iowa, Iowa City, IA

Abstract: In addition to its renal and cardiovascular functions, angiotensin signaling is thought to be responsible for the increases in salt and water intake caused by hypovolemia. However, it remains unclear whether these behaviors require angiotensin production in the brain or liver. Here, we use in situ hybridization to identify tissue-specific expression of the genes required for producing angiotensin peptides, then use conditional genetic deletion of angiotensinogen (Agt) to test whether production in the brain or liver is necessary for sodium appetite and thirst. In the mouse brain, we identified expression of Agt (the precursor of all angiotensin peptides) in a large subset of astrocytes. We also identified Ren1 and Ace (enzymes required to produce angiotensin II) in the choroid plexus, and Ren1 in neurons within the nucleus ambiguus compact formation. In the liver, we confirmed that Agt is expressed in widespread hepatocytes. We next tested whether thirst and sodium appetite require angiotensinogen production in astrocytes or hepatocytes. Despite virtually eliminating expression in the brain, deleting astrocytic Agt did not reduce thirst or sodium appetite. Despite markedly reducing angiotensinogen in the blood, eliminating Agt from hepatocytes did not reduce thirst or sodium appetite, and in fact, these mice consumed the largest amounts of salt and water after sodium deprivation. Deleting Agt from both astrocytes and hepatocytes also did not prevent thirst or sodium appetite. Our findings suggest that angiotensin signaling is not required for sodium appetite or thirst and highlight the need to identify alternative signaling mechanisms.

Disclosures: L. Peltekian: None. **S. Gasparini:** None. **F.S. Fazan:** None. **S. Karthik:** None. **G. Iverson:** None. **J.M. Resch:** None. **J.C. Geerling:** None.

Poster

PSTR286. Ingestion and Energy Balance: Integration of Peripheral Signals

Location: WCC Halls A-C

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Program #/Poster #: PSTR286.24

Topic: F.08. Food and Water Intake and Energy Balance

Support: ADA Pathway to Stop Diabetes Award
ADA Innovative Basic Sciences Award
Russ Berrie Foundation - Obesity Award
New York Nutrition and Obesity Research Center - Pilot Award

Title: Brainstem neurons regulating energy balance

Authors: *A. NECTOW;
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Abstract: The brainstem plays a key role in the sense-and-respond network regulating energy balance. However, the molecular, cellular, and circuit mechanisms through which the CNS achieves this goal is incompletely understood. In recent work, we have demonstrated a key role for the dorsal raphe nucleus (DRN) in regulating balance. Here, using single cell-resolved transcriptional and translational phenotyping, we further characterize the molecular composition of inhibitory and excitatory DRN neurons. We subsequently relate this molecular heterogeneity to their diverse behavioral and physiologic functions, further clarifying the DRN's diverse contributions to energy homeostasis. In particular, we find that these neurons track various aspects of ingestion and that these molecularly distinct populations use aversive drive states to suppress or augment food intake. These findings identify new strategies through which the brainstem regulates feeding. Together, this work represents an important step towards linking hunger to its physiologic and behavioral consequences.

Disclosures: A. Nectow: None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.01/KK13

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIDDK (R01 DK124501)
Klarman Family Foundation Eating Disorders Research Grants Program (Grant ID 4770)

Title: Pkc-delta neurons in the central extended amygdala regulate energy expenditure behaviors

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Abstract: Neurons expressing protein kinase C-δ (PKC-δ) in two specific regions of the central extended amygdala (EAc), namely the central amygdaloid nucleus (CeA) and the oval region of the bed nucleus of the stria terminalis (ovBNST), are known to regulate anorexigenic behaviors. Previous studies have demonstrated that acute activation of these neurons suppresses food intake and, correspondingly, they are necessary for anorexia induced by certain signals such as satiety or inflammation. However, recent findings from our lab have revealed that EAc-PKC-δ neurons are required for female C57BL/6 mice to develop increased running wheel activity during the light period, including food-anticipatory activity (FAA), that occurs under conditions of daily restricted feeding. PKC-δ-Cre mice with ablated EAc-PKC-δ neurons do not significantly increase light period wheel activity upon food restriction compared to ad libitum fed controls, in contrast to WT mice ($p<0.001$, $n = 10$ mice per group). To further test if EAc-PKC-δ neurons

also play a role in regulating energy output-related behaviors, we employed chemogenetic methods to investigate the impact of acute manipulation of EAc-PKC-δ neurons on mouse running wheel activity. Our results show that activation of EAc-PKC-δ neurons during the resting period (light cycle) resulted in elevated wheel activity compared to control mice, while silencing these neurons during the active period (dark cycle) showed a trend towards reduced wheel activity. Additionally, using miniaturized microendoscope calcium imaging in behaving mice, we demonstrated CeA-PKC-δ neurons respond to wheel running activity, and that these dynamics are modulated across days of food restriction. These findings directly link the activity of EAc-PKC-δ neurons to energy expenditure behaviors, indicating that their functional role in energy balance extends beyond energy intake.

Disclosures: **W. Schnapp:** None. **M.B. Schmit:** None. **C. Johnson:** None. **H. Cai:** None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

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Program #/Poster #: PSTR287.02/KK14

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant DK105510
NSF Grant 1652060

Title: Noxious predator odorants cause activation of appetite-suppressing parasubthalamic nucleus (PSTN) neurons

Authors: Z. KAEGI, *M. CARTER;
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Abstract: Feeding and fear behaviors are important for promoting survival in animals. These behavioral phenomena are associated, as animals engaging in fear behaviors are not likely to seek food. Not surprisingly, brain regions that mediate fear responses also influence feeding suppression. One such appetite-suppressing brain region, the parasubthalamic nucleus (PSTN), has been demonstrated to be sensitive to odors and may mediate the suppression of feeding induced by fearful environmental stimuli such as predator odorants. However, it is unknown whether the PSTN is sensitive to a variety of odorants and whether this activation might cause suppression of feeding. We used fiber photometry to test the effects of exposure to eight aversive, attractive, and neutral odorants on activity in PSTN neurons in mice. We found that 2MT and TMT, odorants in predator urine that activate transient receptor potential ankyrin 1 (TRPA1) chemoreceptors in the vagal and trigeminal pathways, induced activation of PSTN neurons over several minutes. In contrast, odorants that engage other olfactory pathways did not cause PSTN activation. Consistently, only predator odorants caused a reduction in food intake. Taken together, these results indicate that appetite-suppressing PSTN neurons are activated by predator odorants.

Disclosures: **Z. Kaegi:** None. **M. Carter:** None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.03/KK15

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH/NINDS OD010996

Title: Leptin-evoked activation of distinct neuronal subpopulations in the centrally projecting Edinger-Westphal nucleus

Authors: ***S. L. HERNAN**, A. F. SVED, G. CANO;
Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: We have proposed that the centrally projecting Edinger-Westphal nucleus (EWcp) integrates signals from diverse central pathways involved in metabolic control and thermoregulation, and adjusts the sympathetic output to multiple organs, including adipose tissues, to help to maintain homeostasis after changes in energy status. The adipose-derived hormone, leptin, signals central targets to regulate energy balance. The EWcp expresses leptin receptors (LepR), and it is part of the central circuitry involved in the control of adipose tissues. It has been reported that the effect of leptin in EWcp on feeding behavior is mediated by peptidergic neurons, mainly containing urocortin-1 and cocaine-and-amphetamine regulated-transcript (CART). Nevertheless, the effect of leptin in non-peptidergic neurons in EWcp (mostly VGluT2 neurons) has not been examined. To characterize EWcp activation in response to leptin, rats were fasted for 24 hours and injected with leptin i.p. (400 ug/kg, n=4 or 800 ug/kg, n=3), and perfused 90 minutes later. Brain sections were processed immunohistochemically to label CART, Fos, and pSTAT3 (only expressed in neurons directly responsive to leptin, i.e., containing LepR). Fos and pSTAT3 expression were quantified in peptidergic (CART) and non-peptidergic (non-CART) neurons in EWcp. Brain regions that express pSTAT3 were also assessed. In situ hybridization (ISH) for LepR, VGluT2, and CART was performed to identify the phenotypes of LepR-expressing neurons in EWcp. There was no effect of leptin dose on the % of Fos-expressing CART ($p=0.71$) and % of Fos-expressing non-CART ($p=0.92$) neurons, so the data was compiled. EWcp activation in response to leptin i.p. induced Fos expression in CART neurons (43.4 ± 2.2%; % CART-Fos/Fos) and in non-CART neurons (56.6 ± 2.2%; % non-CART-Fos/Fos). Of the total CART neurons in EWcp, 30.7 ± 4.7% were activated in response to leptin i.p. (% CART-Fos/CART). pSTAT3 signal was not observed in EWcp but was present in other brain areas known to express LepR, such as the arcuate and ventromedial hypothalamic nuclei. ISH showed that LepR in the EWcp are mainly localized in glutamatergic (VGluT2) neurons (~80% of VGluT2 neurons express LepR), and to a much lesser extent in peptidergic neurons (~10% of CART neurons express LepR). This observation, combined with the Fos data in non-CART neurons, suggests that the glutamatergic subpopulation in EWcp is

substantially activated following leptin i.p. administration. Though most functional studies of EWcp focus on its peptidergic neurons, our results support that the glutamatergic, non-peptidergic population plays a role in leptin-mediated metabolic functions.

Disclosures: S.L. Hernan: None. **A.F. Sved:** None. **G. Cano:** None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

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Program #/Poster #: PSTR287.04/KK16

Topic: F.08. Food and Water Intake and Energy Balance

Support: CIHR PJT-1780036
McGill University Faculty of Medicine Laszlo & Etelka Kollar Fellowship
PhD Fellowship
Healthy Brains for Healthy Lives PhD Fellowship

Title: Central mechanisms underlying MDMA induced hyponatremia in rats

Authors: *J. C. WYROSDIC, Z. S. THIROUIN, C. BOURQUE;
Neurol. & Neurosurg., Res. Inst. of the McGill Univ. Hlth. Ctr., Montreal, QC, Canada

Abstract: Clinical studies have shown that hyponatremia can be induced by the ingestion of the recreational drug MDMA when combined with a water intake (Baggot et al., 2016). However, the mechanisms by which MDMA induces hyponatremia is unknown. Hyponatremia is a life-threatening condition that causes rapid swelling of the brain. Under the Controlled Drugs and Substances Act, MDMA is a schedule 1 drug and consumption usually occur at dance parties. With a prevalence of 3.5% of young adults 18-25 years old using MDMA in the United States in 2014 (Betzler, Viohl, &Romanczuk-Seiferth, 2017), along with the mainstream marketing of MDMA for PTSD, combined with very serious and potentially deathly side effects makes this substance worthwhile to investigate. Findings could not only aid in MDMA associated hyponatremia but could also provide the foundation clinically for fluid regulation during MDMA assisted psychotherapy. Clinically, ingestion of MDMA has been shown to cause an increase in the hormones vasopressin and oxytocin (Wolf et al., 2006). Therefore, we examined cFos activity in rats, we show that there is an increase in both cFos activation of vasopressin and oxytocin neurons of the supra optic nucleus. Despite the clinical literature, our data shows that an injection of MDMA does not increase in water intake in rats. Interestingly, in line with the human literature, when you combine MDMA with a gastric water load, it is sufficient to drop serum sodium levels to hyponatremic levels i.e. <135mmol/L. Indicating that a water load combined with MDMA is necessary for MDMA induced hyponatremia. Conventionally, MDMA has been shown to increase the amount of serotonin within the synaptic cleft (Oeri, 2021). To determine if MDMA is working via the release of 5HT we utilized whole cell patch clamp slice electrophysiology of double transgenic Wistar rats enabling fluorescent identification of

vasopressin and oxytocin neurons. Interestingly, at a bath temperature of a constant 30*C, a bath application of 5HT was sufficient in causing an enhancement of action potential firing, and this could be blocked by a 5HT receptor antagonist. Moreover, a bath application of MDMA also caused an increase in action potential firing, which too could be blocked by a 5HT receptor antagonist.

Disclosures: **J.C. Wyrosdic:** None. **Z.S. Thirouin:** None. **C. Bourque:** None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.05/KK17

Topic: F.08. Food and Water Intake and Energy Balance

Support: UVA Brain Institute Fellowship to AW
NIH R01 HL153916 to JC
American Diabetes Association Pathway to Stop Diabetes Initiator Award 1-18-INI-14 to JC

Title: Unraveling the Neural Circuitry of Energy Balance with Molecular Connectomics

Authors: *A. N. WEBSTER[1], D. C. SCHWALBE[2], E. N. GODSCHALL[2], A. D. GULER[2], J. N. CAMPBELL[2,1];
[1]Neurosci. Grad. Program, [2]Dept. of Biol., Univ. of Virginia, Charlottesville, VA

Abstract: Identifying neurons which are synaptically connected is a fundamental challenge in neuroscience, especially in the hypothalamus, a heterogeneous region which controls appetite and other functions through largely obscure neural circuits. One method for identifying synaptically connected neurons uses a fluorescent-labeling rabies virus, modified so that it can only infect a target population of neurons and their presynaptic partners. This method can anatomically and morphologically identify presynaptic partners but otherwise provides little insight into their identity. We therefore developed a method which leverages monosynaptic rabies with single-cell transcriptomics to molecularly identify connected neurons. To demonstrate its utility, we applied our method to neurons in the arcuate hypothalamus(ARC) that express Agouti-related peptide (AgRP) and regulate appetite and metabolism, but for whom only a few presynaptic partners are known. Following infection of AgRP neurons and their presynaptic partners with rabies-H2b-mCherry, we isolated mCherry+ cell nuclei from the ARC, dorsomedial hypothalamus, and paraventricular hypothalamus. We then profiled their transcriptomes by single-nuclei RNA-sequencing (5770 cells, averaging 2296 genes/cell) and mapped the ARC transcriptomes onto a previously published dataset made from uninfected ARC neurons. Rabies significantly altered expression of 328 genes in AgRP neurons, relative to those only infected with AAV. However, 75% of subtype specific genes were not significantly affected by rabies, supporting our ability to identify rabies-infected neurons. Overall, our results reveal 14

candidate afferent populations of AgRP neurons within the ARC. Our results confirm previously identified sources of synaptic input, including Kisspeptin-Neurokinin B-Dynorphin (KNDy) neurons and dopaminergic (*Th*+/*Slc6a3*+) ARC neurons. Our results also suggest 12 other ARC cell populations synapse onto AgRP neurons, 5 of which we validated using RNA fluorescence in situ hybridization. Among these are inhibitory neurons which express receptors for leptin and glucagon-like peptide 1 and so may couple those signals to satiety by inhibiting AgRP neurons.Identifying these afferent populations will shed light on the circuits and signaling pathways which shape AgRP neurons' role in energy balance. In addition, our method can be applied to any molecular neuron subtype to identify presynaptic partners in a versatile and genetically tractable way.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

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Program #/Poster #: PSTR287.06/KK18

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIDDK Mentored Clinical Scientist Research Career Development Award, 1K08DK132493-01A1

Title: Novel method for whole brain analysis of internal states reveals network interactions between hunger state and sensory cues

Authors: L. ROGERSON, *A. RAMIREZ, D. SALZMAN;
Columbia Univ., New York City, NY

Abstract: Neural circuits that have evolved to maximize food seeking behavior communicate extensively with the body to keep metabolism within a tight range. Consequently, sensory, motor, and reward pathways in the brain are modulated by internal states indicative of energy balance; notably, hunger and satiety. These distributed networks are challenging to isolate because they are spatially intermingled but functionally distinct. To overcome this challenge, we developed a novel method for achieving two timepoint labeling and statistical inference in rodents, allowing us to study whole brain activity at a single cell resolution. Building upon our previous investigation of whole-brain networks during fasting and refeeding, we now employ the same methodology to delve into the realm of palatable food perception. Our focus is on evaluating neuronal activity in response to food cues, specifically examining how hunger state modulates these responses within a single animal. Not only does this approach enable us to compare the intricate neural responses to palatable food after fasting and refeeding, but also the nuanced differences in responses between palatable food and regular chow. This knowledge may

offer valuable insights into the development of targeted interventions for obesity and metabolic disorders.

Disclosures: **L. Rogerson:** None. **A. Ramirez:** None. **D. Salzman:** None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

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Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant T32DK112751
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Title: Chemogenetic activation of a subset of VMHvl ERα-positive neurons co-expressing Mc4r increases energy expenditure and improves glucose tolerance

Authors: *G. DENG[1,2], Y. DENG[2], J. JIANG[2], U. SINGH[2], L. SCHMIDT[2], Z. ZHU[3], L. ZINGMAN[4], H. CUI[5];
[2]Neurosci. and Pharmacol., [1]Univ. of Iowa, Iowa City, IA; [3]Intrnl. Med., Univ. of Iowa, University of Iowa, IA; [4]Intrnl. Med., Univ. of Iowa, Iowa City, IA; [5]Neurosci. and Pharmacology, Iowa Neurosci. Institute,, Univ. of Iowa Roy J and Lucille A Carver Col. of Med., Iowa City, IA

Abstract: Obesity remains a pressing public health concern worldwide. The ventromedial nucleus of the hypothalamus (VMH) is a sexually dimorphic brain nucleus consisting of heterogeneous cell types that collectively play integral roles in metabolic regulation. Neurons in the ventrolateral region of the VMH (VMHvl) that express the estrogen receptor alpha (ERα) have been implicated in glucose and body weight homeostasis in a sex-specific manner. Notably, a subset of these VMHvl ERα+ neurons co-express the melanocortin-4 receptor (Mc4r), a well-known gene associated with obesity. Given the established role of both ERα and Mc4r signaling in metabolic homeostasis, we hypothesized that these Mc4r+/ERα+ VMHvl neurons sex-specifically contribute to metabolic control. To test this hypothesis, we crossbred male mice expressing Flp recombinase in ERα+ cells (ERα-Flp+) with female Mc4r-Cre+ mice, generating ERα-Flp+/Mc4r-Cre+ double transgenic mice for an intersectional chemogenetic approach. Subsequently, these double transgenic mice received microinjection of an AAV expressing an excitatory chemogenetic receptor (hM3Dq) in Cre- and Flp-dependent manner into the VMHvl, allowing us to specifically target and activate this specific subset of VMHvl ERα+ neurons chemogenetically for functional investigation. Following intraperitoneal administration of the chemogenetic ligand deschloroclozapine (DCZ), these double transgenic, but not wild-type, mice exhibited significantly increased brown adipose tissue temperature and locomotor activity compared to vehicle treatment, particularly in male mice. Follow-up whole-body indirect calorimetry and plethysmography confirmed that chemogenetic activation of these ERα+/Mc4r+

VMHvl neurons markedly increase energy expenditure (EE) and respiration, more profoundly in male mice. Additionally, consistent with the reported roles of VMHvl ERα+ neurons in glucose-sensing and glycemic control, we found that chemogenetic activation of Mc4r+/ERα+ VMHvl neurons significantly improve systemic glucose tolerance in both sexes. Collectively, our results identify this distinct subset of VMHvl ERα+ neurons expressing Mc4r as an important sexually dimorphic regulator of EE and glucose homeostasis.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

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Topic: F.08. Food and Water Intake and Energy Balance

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Cooperative Study Program of the National Institute for Physiological Sciences 19-256
Graduate Program of Transformatige Chem-Bio Research in Nagoya University

Title: Gpr75 signaling isndispensable for reproductionbut involvedin high-fat diet-induced feeding and hyperglycemia in rats

Authors: *Y. OTSUKA[1,2], N. INOUE[2], M. HIRABAYASHI[3], H. TSUKAMURA[2], Y. UENOYAMA[2];
[1]Amimal science, Univ. of Nagoya, Nagoya, Japan; [2]Amimal science, Nagoya university, Nagoya, Japan; [3]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: A recent study showed that haploinsufficiency of G-protein coupled receptor 75 (GPR75) gene (*Gpr75)* caused lower body weight in humans, suggesting that GPR75 could be a potential therapeutic target to prevent obesity (Akbari et al., 2021). The present study aimed to examine the role of GPR75 signaling in controlling feeding, metabolism, and reproduction using newly generated *Gpr75* knockout (KO) rats. We found that *Gpr75* mRNA expression was highly detected in the hypothalamus, while the expression was limited in other peripheral tissues in female rats. Both female and male *Gpr75* KO rats exhibited significantly lower body weight and food intake compared to wild-type (WT) control rats. On the other hand, there were no differences in the timing of puberty onset or pulsatile luteinizing hormone secretion between

Gpr75 KO and WT groups in both sexes. Next, male *Gpr75* KO or WT rats were subjected to a high-fat diet (HFD) or control diet (CONT) feeding. The body weight and food intake of HFD-fed WT rats were significantly higher than those of CONT-fed WT rats, whereas the body weights and food intake of HFD- and CONT-fed *Gpr75* KO rats were significantly lower than those of HFD- and CONT-fed WT rats. Furthermore, the quantitative analysis of mRNA expression of some orexigenic and anorexigenic neuropeptides in the hypothalamus of male rats revealed that mRNA levels of hypothalamic agouti-related peptide (AgRP) were significantly higher in *Gpr75* KO rats than in WT rats regardless of types of diets, suggesting that GPR75 plays a role in the downstream of orexigenic AgRP signaling and that *Gpr75* KO may prevent AgRP-induced feeding. In addition, a glucose tolerance test revealed that plasma glucose and insulin levels were significantly lower in HFD-fed *Gpr75* KO rats than in HFD-fed WT rats. Regardless of type of diet, C-C motif chemokine ligand 2 (CCL2, an inflammatory marker) mRNA expression was significantly lower in the gonadal white adipose tissue (gWAT) of *Gpr75* KO rats compared to WT rats. Moreover, mRNA level of adiponectin, a peptide which promotes glucose uptake, was significantly lower in the gWAT of CONT-fed *Gpr75* KO rats compared to CONT-fed WT rats. These results suggest that GPR75 may mediate the orexigenic effect of AgRP signaling and then promote feeding, obesity, hyperglycemia, and insulin resistance induced by HFD. Therefore, drug discovery of antagonists targeting GPR75 may contribute to developing new therapeutic techniques that control feeding and body weight and improve insulin resistance without affecting reproduction.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

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Program #/Poster #: PSTR287.09/LL1

Topic: F.08. Food and Water Intake and Energy Balance

Title: Activation of α7nAChR Modulates Body Weight, Anxiety-like Behaviors, and Nociception in Murine Diet-induced Obesity

Authors: *S. ALSHARARI[1], A. A. ALAMEEN[1], F. ALDAFIRI[1], F. A. ALOTAIBI[1], Y. SALAH[1], M. A. ALSHAMMARI[2], Y. SARI[3], M. I. DAMAJ[4];
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Abstract: Background: Obesity becomes a major health issue of the current century and it has a detrimental effect on all physiological functions promoting disorders including anxiety and pain hypersensitivity. Several studies report that acute and chronic exposure to palatable diet induced obesity associated with neuro-inflammation. Cholinergic anti-inflammatory pathways relieve

inflammation via α7 nicotinic acetylcholine receptor (α7nAChR) signaling. Since the currently approved pharmacological drugs are linked to serious side effects, searching for novel targets is mandatory. In this regard, α7nAChR might serve as a promising therapeutic target in fighting against obesity and obesity associated disorders.**Objectives**: the present study aimed to assess body weight changes and anxiety-like behaviors associated with chronic exposure to obesogenic diet in male C57BL/6J.**Method**: Initially, mice (n=8/group) exposed to either standard chow alone in the control group or plus obesogenic diet in the obese group to for 7 weeks to induce obesity. Metabolic parameters were measured regularly then treatments [vehicle, PNU-282987 hydrate (α7nAChR agonist), and methyllycaconitine citrate (MLA, α7nAChR antagonist)] were given to examine changes in metabolic and behavioral parameters.**Results**: On day42, mice exposed to obesogenic diet showed significantly higher food intake over those administered standard chow (23.13 VS 9.77 Kcal/day, P-value= 0.0004) and they significantly gained more weight from initial (25.5 Vs 16.15 %, P-value= 0.0026). Treating obese mice with PNU-282987 normalized the food intake (P-value < 0.0001) while MLA block this effect. Moreover, anxiety-like behavior assessment showed significantly higher anxiety in obese mice in comparison to control group showed less time spent in open arms (26.06 VS 60.966 sec, P-value=0.0004) and lower time in light compartment (109.4 VS 130.97 sec, P-value= 0.0167) using elevated plus maze and light and dark paradigms, respectively. However, introducing PNU significantly alleviate anxiety-like behavior by increasing the time spent in open elevated arm and light compartment (up to 84.84, P-value=0.0002 and to 136.63, P-value= 0.0082), correspondingly.**Conclusion**: exposing male mice to obesogenic diet displayed gain weight, and anxiety-like behavior, while pharmacological activation of α7nAChR alleviate weight gain and obesity-associated disorders.

Disclosures: S. Alsharari: None. **A.A. Alameen:** None. **F. Aldafiri:** None. **F.A. Alotaibi:** None. **Y. Salah:** None. **M.A. Alshammari:** None. **Y. Sari:** None. **M.I. Damaj:** None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.10/LL2

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH/NINDS OD010996

Title: Connections of the Edinger-Westphal nucleus with the central circuitry that controls the sympathetic outflow to adipose tissues

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Abstract: The centrally projecting Edinger-Westphal nucleus (EWcp) is anatomically and functionally distinct from the EW nucleus that contains parasympathetic preganglionic neurons

involved in pupillary constriction. We have proposed that EWcp contributes to the control of energy homeostasis via modulation of sympathetic outflow to multiple organs, including adipose tissues, after integrating multimodal signals from central systems involved in thermoregulation and metabolic control. To characterize the central pathways that link EWcp with adipose tissues, we injected combinations of viral tracers in EWcp and brown (BAT) or white (WAT) adipose tissues. Rats were injected with an anterograde herpesvirus expressing mCherry (stHSV) in EWcp and a retrograde transynaptic pseudorabies virus expressing GFP (PRV-152) in BAT (n=4) or WAT (n=3) to identify neuronal groups involved in fat control (PRV-infected) that receive afferent inputs from EWcp (stHSV-fibers). After appropriate survival times, rats were perfused. Brain sections were processed immunohistochemically to label infected neurons and fibers. There were afferent fibers from EWcp in apposition to BAT- or WAT-infected presympathetic neurons in the paraventricular hypothalamic nucleus (PVN), A5 group, locus coeruleus, ventromedial medulla (VMM), rostral (RVLM) and caudal (CVLM) ventrolateral medulla. In the forebrain, fibers from EWcp were observed on BAT- or WAT-infected neurons in regions involved in BAT-mediated thermoregulation, such as the preotic area (POA), lateral hypothalamus (LH), arcuate, dorsomedial hypothalamic, and tuberomammilary (TMN) nuclei. There were also a few anterograde stHSV-infected neurons in all these areas, indicating that EWcp neurons are synaptically connected to BAT- and WAT-infected neurons. Another group of rats was injected with a PRV expressing RFP (PRV-614) in BAT and PRV-152 in EWcp (n=6) to identify EWcp afferents that are also part of the circuit that controls the sympathetic outflow to BAT. Double-infected neurons were found in the POA, PVN, LH, habenula, TMN, A7 and A5 group, VMM, RVLM, CVLM and nucleus of the solitary tract. Our results demonstrate the existence of a complex circuit directly linking EWcp and its afferents with neuronal groups that control adipose tissue activity, with multiple reciprocal connections, suggesting a highly interconnected circuit. These data provide a neuroanatomic substrate for a putative role of EWcp as a hub that integrates multiple inputs from regions involved in the control of adipose tissues, and conveys the appropriate output to presympathetic groups that, in turn, modulate the sympathetic outflow to these tissues.

Disclosures: G. Cano: None. **S.L. Hernan:** None. **A.F. Sved:** None.

Poster

PSTR287. CNS Control of Ingestion and Energy Balance

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Topic: F.08. Food and Water Intake and Energy Balance

Support: NIMH Grant R01 MH119089- 01
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Title: Control of feeding by a bottom-up midbrain-subthalamic pathway

Authors: F. M. C. V. REIS[1], S. MAESTA-PEREIRA[1], M. OLLIVIER[2], P. J. SCHUETTE[1], E. SETHI[1], ***B. A. MIRANDA**[1], E. INIGUEZ[1], M. CHAKERIAN[1], E. VAUGHN[4], M. SEHGAL[3], D. C. T. NGUYEN[1], F. T. H. YUAN[1], A. TOROSSIAN[1], J. M. IKEBARA[5], A. H. KIHARA[5], A. SILVA[6], J. KAO[7], B. KHAKH[8], A. ADHIKARI[1];
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Abstract: Investigative exploration and foraging leading to food consumption have vital importance, but are not well-understood. Since GABAergic inputs to the lateral and ventrolateral periaqueductal gray (l/vlPAG) control such behaviors, we dissected the role of vgat-expressing GABAergic l/vlPAG cells in exploration, foraging and hunting. To investigate how l/vlPAG vgat cells encode exploratory approach towards food and eating, we injected the vector AAV-DIO-GCaMP6s in the l/vlPAG of vgat cre mice to express the genetically encoded calcium indicator GCaMP6s in l/vlPAG vgat cells. This approach allowed us to obtain calcium transients from these cells through miniaturized microscopes as freely-moving mice forage for both highly palatable food (walnut) and prey (cricket). Both approach and eating behaviors could be decoded above chance levels in cricket and walnut assays using calcium transient activity as model input (n=4; one-sample t-test, cricket t-statistics: approach=3.87, eat=5.59; walnut t-statistics: approach=4.75, eat=7.53). We then manipulated the activity of l/vlPAG vgat cells *in vivo* during foraging through expression of inhibitory opsin archearhodopsin (n=7) and excitatory channelrhodopsin (n=9) while control mice express YFP (n=6). Inhibition of these cells decreased the amount of walnut eaten and increased latency to predate; excitation decreased latency to eat walnut, increased amount eaten, and decreased latency to predate. Given this data, we hypothesized that the vgat l/vlPAG cells would be interconnected with other known feeding regions. Both retrograde and anterograde circuit mapping revealed dense interconnectivity between the PAG and feeding regions, such as the medial preoptic area, the central amygdala, the lateral hypothalamic area, the bed nucleus of the stria terminalis and the zona incerta (ZI); the strongest downstream projection was seen in the ZI. We now identify a previously uncharacterized monosynaptic GABAergic projection from l/vlPAG vgat cells to the ZI. Fiber photometry recordings show that both in the walnut and the cricket assay, this projection was more active prior to eating onset. Optogenetic manipulation of the axon terminals of this projection robustly increases foraging and predation, suggesting the existence of a novel, bottom-up midbrain mechanism controlling feeding.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.12

Topic: F.08. Food and Water Intake and Energy Balance

Support: Novo Nordisk
National Institute of Diabetes and Digestive and Kidney Diseases
Copenhagen University

Title: The Role of Area Postrema Calcr Expressing Neurons in the Control of Food Intake

Authors: *D. GORDIAN[1,2], M. A. MENSAH[6], S. KERNODLE[3], A. PUTTAIAH[4], M. G. MYERS[4,5,2];
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Abstract: Title: The Role of Area Postrema *Calcr*- Expressing Neurons in the Control of Food Intake
Authors: Desiree Gordian[1,2], Mike Ayensu-Mensah[3], Stace Kernodle[4], Anika Puttaiah[5], and Martin G. Myers[1,2,5]
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Abstract: Signals from the gut and elsewhere act in the dorsal vagal complex (DVC) to promote meal termination and mediate aversive responses to gastrointestinal malaise. Of the DVC brain regions, molecularly identified neuron populations of the area postrema (AP, which lies dorsal to the *nucleus tractus solitarius* (NTS) and the dorsal motor nucleus of the vagus (DMV)) remain relatively unstudied due to the difficulty of stereotaxically targeting them in mice. To understand the circuitry and function of AP neurons that express the calcitonin receptor (*Calcr*), we generated a *Calcr*^{Cre} rat model. Intra-AP injection of viruses to cre-dependently express synaptic tracers in these animals revealed projections mainly to the NTS, DMV, and the lateral parabrachial nucleus (lPBN), where projections from AP *Calcr* neurons terminated in a region distinct from aversive CGRP cells. We also injected an AAV to cre-dependently express the activating (hM3Dq) Designer Receptor Exclusively Activated by Designer Drugs (DREADD) into the AP of *Calcr*^{Cre} rats to permit the activation of transduced *Calcr* neurons by the administration of CNO. *Post hoc* analysis revealed two classes of animals with transduced DVC neurons- those that expressed hM3Dq only in AP Calcr neurons (Calcr$^{AP\text{-}Dq}$ rats) and those in which some virus leaked into the NTS, as well (Calcr$^{AP+NTS\text{-}Dq}$ rats). CNO treatment decreased short-term food intake and delayed gastric emptying without provoking conditioned taste avoidance in Calcr$^{AP\text{-}Dq}$ and Calcr$^{AP+NTS\text{-}Dq}$ rats. However, multi-day CNO treatment of Calcr$^{AP\text{-}Dq}$ rats failed to reduce body weight. These results suggest that neither AP nor NTS *Calcr* neurons mediate aversive responses and that decreased gastric emptying does not necessarily provoke

aversive responses. Furthermore, while AP *Calcr* cells mediate short-term effects on feeding and do not impact body weight.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.13/LL4

Topic: F.08. Food and Water Intake and Energy Balance

Support: NKFIH KKP 126998
NKFIH K138836
ELKH SA-48

Title: Agrp neurons modulate exploratory behavior

Authors: E. BALKÓ[1], M. KAPILLER[1], F. MATYAS[2], B. BARSY[2], L. DENES[1], P. T. SOTONYI[1], **B. RÁCZ**[3], T. L. HORVATH[4];
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Abstract: Hypothalamic agouti-related peptide (AgRP)-expressing neurons are exclusively located in the arcuate nucleus of the hypothalamus and form the basis of the melanocortin system, a set of CNS circuits regulating energy homeostasis. Besides an important role in driving food intake, AgRP neurons are also involved in modulating complex, non-feeding behaviors. However, it is unknown how AgRP-dependent feeding influences general exploratory behavior. Using the $AgRP^{DTR}$ mouse model with impaired AgRP neuronal functions, we show here that perturbation of AgRP neuronal function leads to sex-dependent altered behavioral responses driven by calorie restriction (CR). Our findings highlight the pivotal role of the AgRP neurons during CR in the regulation of complex behaviors and show that AgRP neurons are critical for complex behavioral adaptations to CR.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.14/LL5

Topic: F.08. Food and Water Intake and Energy Balance

Title: Eating behavior phenotype changes and treatment response to GLP-1 agonist for hypothalamic obesity patients: two prospective studies

Authors: *S. LEE[1], S.-S. PARK[2], M. LEE[3], M.-J. PARK[4], Y. KIM[4], J. KIM[2], H. CHOI[3]; [1]Seoul Natl. Univesity, Seoul, Korea, Republic of; [2]Pituitary Ctr., [3]Biomed. Sci., [4]Neurosurg., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: **Background(objective):**Hypothalamic obesity is a severe, intractable obesity that rapidly occurs when the hypothalamus is damaged by brain therapy. It is primarily known to be caused by craniopharyngioma among brain tumors. There have been attempts to predict the development of obesity by assessing the degree of hypothalamic damage. However, no method has yet been developed to predict and diagnose the development of hypothalamic obesity. Moreover, there is currently no treatment for this condition. We aimed to investigate various phenotypic changes associated with the development of obesity after tumor surgery and to discover the responding subtypes after GLP-1 agonist therapy.**Method:**We performed a prospective study with 50 patients (aged 19 yr or older) who have been diagnosed and treated surgically with a hypothalamic tumor or a nonfunctioning pituitary tumor. Several subscale results were collected with basic clinical information, tumor size, physical measurements, digital food diary, wearable device measurement, appetite/satiety/eating behavior assessments (questionnaires), cognitive behavioral task assessments, and biochemical test results related to obesity. Comparisons were statistically conducted between the patient's pre-operative and post-operative assessment to observe the development of postoperative obesity. In addition, we performed a prospective study with GLP-1 agonist (Saxenda) treatment in patients with hypothalamic damage (HD) (craniopharyngioma) to investigate treatment response.**Results:**Patients with hypothalamic damage and large tumor size showed higher post-operative weight gain than other patients. These patients had higher restrained eating behavior, emotional eating behavior, and higher average daily kcal intake after the surgery. The results of GLP-1 agonist administration and predictors of the treatment response are analyzed.**Conclusion:**These results suggested that tumor size is related to hypothalamic damage, post-operative weight gain, and eating behavior changes. This study identified factors associated with the development of obesity, which may provide a clinical basis for understanding the pathophysiological mechanisms of hypothalamic obesity.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

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Program #/Poster #: PSTR287.15/LL6

Topic: F.08. Food and Water Intake and Energy Balance

Support: JHU Summer PURA Grant 2022
NIH grant R00 DK088360
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Kirby Center for Functional Brain Imaging P41 EB015909-19

Title: The Role of Cerebellum in Eating Behavior

Authors: *Y. ZHOU, G. THAPALIYA, L. CHEN, S. CARNELL;
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Abstract: Neuroimaging techniques such as functional Magnetic Resonance Imaging (fMRI) have provided valuable insights into the neurobiology underlying variation in eating behavior among humans. Food cues are one of the key environmental stimuli influencing eating behavior. Understanding altered food cue responsivity and resting state connectivity within neural systems subserving appetite in individuals with obesity and eating-related pathology may help inform the development of neurobehaviorally-targeted interventions. A recent reverse-translational study uncovered a role for anterior deep cerebellar nuclei in satiation, suggesting functioning in the cerebellum may contribute to eating behavior. We aimed to investigate the extent, range and nature of cerebellar activation to food cues, as well as functional connectivity of the cerebellum to other brain regions in the resting state, in published fMRI studies of obesity and eating disorders. Pubmed and Google Scholar were systematically searched up to September 2022 using keywords including cerebellum [and] food cue / go-no-go / obesity / eating disorders / appetite. Studies were eligible for inclusion if they reported outcomes of either a food cue fMRI task or resting-state fMRI. We identified 11 food cue fMRI studies reporting cerebellum effects. Of these, 7 reported food vs non food differences, 3 reported high vs low calorie food differences, and 1 reported a difference in food cue responses between fed and fasted states. 3 reported differences in cerebellum responses between individuals with obesity vs healthy-weight, 3 reported differences in cerebellum responses between individuals with eating pathology (1 Anorexia Nervosa, 2 Prader-Willi Syndrome) vs. healthy-weight, 1 reported differences in cerebellum responses post vs pre bariatric surgery, and 2 reported differences in cerebellum responses after leptin administration in leptin-deficient patients. We identified 6 studies reporting cerebellar functional connectivity findings. Of these 2 studies reported differences by weight status, and 4 reported differences by eating pathology (2 Anorexia Nervosa, 1 bulimia nervosa, 1 evening hyperphagia). Charting peak coordinates of implicated regions demonstrated effects throughout the anterior, posterior, and flocculonodular lobes of the cerebellum that were on the whole not consistent within type of study, likely due in part to methodological variation between studies. Our results support a role for the cerebellum in eating behavior, and argue for more rigorous research to investigate potential differentiation of function with relevance to eating behavior within the cerebellum.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.16/LL7

Topic: F.08. Food and Water Intake and Energy Balance

Title: Disruption of Transient Receptor Potential Channel 5 Causes Obesity

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Abstract: Background: The prevalence of obesity has increased worldwide. More than one-third of the population is obese and therefore at risk of developing type 2 diabetes, which has a great impact on health and economy. Transient Receptor Potential Channel 5 (TRPC5) is a brain-expressed, membrane-spanning cation channel, which regulates the depolarization of neurons involved in energy homeostasis in rodents. **Methods:** We used CRISPR-Cas9 approach to generate a knock-in Trpc5 mutation mouse and examined the metabolic change. We also used designer receptor exclusively activated by designer drugs (DREADD) to inhibit POMC neuron activity and test the effect of Trpc5 activator in food intake. Lastly, we deleted Trpc5 in oxytocin neurons and examined the phenotype using Cre-LoxP system. **Results:** Knock-in male and female mice harboring a human loss-of-function *TRPC5* mutation exhibited obesity and hyperphagia. POMC neurons express abundant Trpc5 and BTD (Trpc5 activator) can reduce food intake in mice through activating POMC neurons. Importantly, chemogenetic inactivation of hM4Di-expressing POMC neurons with clozapine N-oxide (CNO) blocked BTD-induced anorexia. Meanwhile, we also found oxytocin neurons in paraventricular hypothalamic (PVH) express abundant Trpc5. Deletion of Trpc5 in oxytocin neurons significantly increased food intake and body weight, associated with hyperglycemia. Moreover, acute treatment with oxytocin decreases body weight and improves glycemic control in knockout mice. **Conclusions:** These results demonstrated that genetic disruption of TRPC5 in leads to intense food seeking and obesity, which suggesting that TRPC5 play a vital role in obesity and may become a novel target for human obesity treatment.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

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Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251 to AMK
PRELS Fellowships to LSA and MQ
RISE Fellowship to VIN
Eloise E. and Patrick Wieland Fellowship to KN

Title: Comparison of the inputs and outputs of the anterior subdivisions of the lateral hypothalamic area in the adult male rat using an open-access atlas framework

Authors: *L. SOTO ARZATE[1], M. QUINTANA[1], V. I. NAVARRO[1], K. NEGISHI[1,2], A. M. KHAN[1];
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Abstract: Neuroanatomical tracing studies of the cytoarchitectonically-derived subdivisions of the lateral hypothalamic area (LHA) have yielded connectional differences that support the idea proposed by Swanson (2018; *Brain Maps 4.0* (*BM4.0*) *J. Comp. Neurol.*) for their existence as separately parceled cell groups. Our laboratory has previously conducted tracing studies that explored the hodological differences between the dorsal and anteroventral subdivisions of the LHA and found that each of these differs sufficiently to justify their separation. In an effort to add to these studies, we aimed to compare the labeling patterns produced by two cocktail injections of retrograde and anterograde tracers, cholera toxin B subunit and *Phaseolus vulgaris*-leucoagglutinin (PHAL), respectively, within the LHA ai/ad and LHAav, across levels 5-40 of *BM4.0* to visualize the connectional patterns between these subregions. Preliminary results suggest marked differences in their connectional profiles. Although anterograde transport of PHAL from both injections are very similar, they appear to contrast with each other's subregional distributions. One such instance of this is the lateral septal projections from LHAai/ad, which cover the rostral medial dorsal zone of that nucleus, whereas the injection in the LHAav demonstrates few fibers in this subdivision of the lateral septum. Overall, trends for LHAai/ad targets tend toward more lateral regional distribution, while LHAav targets stay within the medial regions. Some regions of overlap include the lateral habenula and medial septal nucleus. Additionally, a very noticeable feature that distinguishes these two experiments is that the LHAai/ad tends to favor ipsilateral regions for its anterograde projections while the LHAav communicates with regions on the contralateral side. Similarly, retrograde transport follows many of the above-stated trends, which overall underscores how these two regions have very distinct connectional profiles that merit subregional separation.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

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Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251
NSF ASPIRE Fellowship to JSP
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Title: Standardized mapping of glucagon-like peptide 1 (GLP-1) immunoreactive neuronal populations in the hindbrain: immunohistochemical studies in the adult male rat

Authors: *J. V. SALCIDO, Padilla[1], G. P. TAPIA[2], A. M. KHAN[2];
[2]Biol. Sci., [1]The Univ. of Texas at El Paso, El Paso, TX

Abstract: Glucagon-like peptide 1 (GLP-1) is a versatile molecule that is produced peripherally in the L-cells of the intestine and centrally in a population of neurons located in the nucleus of the solitary tract (NTS). A growing body of literature indicates that these neurons send widespread projections to distinct brain regions and that their location in the hindbrain (HB) suggests a role in feeding control and glucose homeostasis. In this study, fixed-frozen brain tissue sections of male Sprague-Dawley rats were processed using a commercially available polyclonal antibody raised against GLP-1, surveyed for GLP-1-like immunoreactivity, and mapped to a standardized open-access atlas of the rat brain (*Brain Maps 4.0* (*BM4.0*); L. W. Swanson, 2018, *J. Comp. Neurol*.) We employed fluorescence immunohistochemistry or 3,3'-diaminobenzidine (DAB) immunoperoxidase staining to visualize and map the precise locations of GLP-1+ neurons in the caudal nucleus of the solitary tract (NTS) within *BM4.0*. To assess validity of signal localization, we also performed control experiments using tissue sections harvested from select forebrain regions immunoreacted with the same antibody and compared our data with that of the existing literature. At *BM4.0* atlas levels 69 and 70, GLP-1 immunopositive cells were observed in the medial (NTSm), commissural (NTSco), and lateral NTS (NTSl). At atlas levels 71-73, GLP-1 immunopositive cells were mostly observed in the NTSco and NTSm. We observed few cells in the ventral medullary reticular nucleus (MDRNv) at this range of levels. Control experiments revealed GLP-1-ir neurites in the lateral hypothalamic area (LHA) and the ventral tegmental area (VTA). These atlas assignments place the GLP-1-expressing cell group within a defined spatial framework in stereotaxic space and will facilitate their precise targeting in future experiments.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

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Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251 to AMK
RISE Fellowship to VIN
Eloise E. and Patrick Wieland Fellowship to KN

Title: High-spatial resolution mapping of bidirectional connections between the lateral septal nucleus and the lateral hypothalamic anterior and dorsal regions in the adult male rat

Authors: *V. I. NAVARRO[1], K. NEGISHI[1,2], I. DELGADO[1], A. M. KHAN[1];
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Abstract: The lateral hypothalamic area (LHA), once regarded as a relatively homogenous brain area, is known to have diverse cell groups involved in a variety of functions. One proposed model of LHA organization, furnished by Swanson, has subdivided the LHA into multiple zones, tiers, and regions based on cytoarchitecture (*Brain Maps 3.0*; 2004). Since then, several studies have shown that these parceled groups harbor cells with distinct connections, reinforcing their status as distinct structural entities. Our own ongoing efforts to independently test this spatial model of organization have led us to identify connections of the anterior and dorsal subdivisions of the LHA (LHAa and LHAd, respectively) using the anterograde and retrograde tracers, *Phaselous vulgaris*-leucoagglutinin and cholera toxin B subunit, respectively (Navarro et al., SfN Global Connectome Meeting abstract, 2020/2021; Toccoli et al., SfN Abstract, 2021). Here we report on studies investigating the neuroanatomical inputs and outputs of the LS and LHAa/d in male rats covering levels 5-40 of *Brain Maps 4.0* (*BM4.0*; Swanson, 2018, *J Comp Neurol*). These connections were mapped at high-spatial resolution within the atlas templates of *BM4.0* to analyze where these regions differ and overlap connections and to bring these data into spatial registry with those that have previously been generated. We found that the lateral septal nucleus (LS) rostral part medial zone ventral region rostral domain (LSr.m.v.r.) appears to not only send projections to the LHAa (as first reported by Risold and Swanson, *Brain Res Rev*, 1997), but also receives inputs from this subregion. Moreover, the LHAd projects to the more dorsal portions of the LS, and our work confirms and extends the findings of Risold and Swanson again by demonstrating bidirectional connections between the structures. These data add to the precise mapping of connections between these two extensively subdivided brain regions. Given the vital roles that the LS and LHA play in regulating reward and feeding, among other functions, our findings provide additional rationale for further detailed exploration of functional communication between these brain regions.

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Poster

PSTR287. CNS Control of Ingestion and Energy Balance

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.20/LL11

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH GM127251
NSF ASPIRE Fellowship to GPT
UTEP College of Science

Title: Atlas-based spatial analysis of the distribution of feeding-associated neuropeptide immunoreactivities within the rat parabrachial nucleus

Authors: *G. P. TAPIA[1], L. LUCERO[2], A. BLAKE[1], S. BALIVADA[2], A. M. KHAN[2];
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Abstract: The rat parabrachial nucleus (PB) is located in the dorsolateral pons and consists of >10 distinct subregions that surround the superior cerebellar peduncle (scp). The PB is understood to play a significant role in the control of food intake and has previously been demonstrated to be activated after refeeding (G Zséli *et al*., *J. Comp. Neurol.*, 2016). Neuronal processes innervating the PB contain diverse feeding-associated neuropeptides, but the chemoarchitecture of PB neuronal populations has not been systematically mapped using an atlas-based approach. To begin addressing this deficit, we processed brain sections containing the PB for immunohistochemistry using antibodies against calcitonin gene-related peptide (CGRP), neurotensin (NT), cholecystokinin (CCK), or oxytocin-associated neurophysin (PS38), and mapped the immunoreactive patterns to an atlas of the rat brain (L. W. Swanson, *Brain Maps 4.0*, *J. Comp. Neurol.*, 2018). Photomicrographs of these sections were aligned with those of an adjacent series of Nissl-stained tissue that served as a cytoarchitectural reference, enabling the data to be mapped to atlas levels with PB representations (Atlas Levels 47-52). Fiber density distributions were plotted for each neuropeptide and the spatial distribution among the populations was compared. CGRP-immunoreactive fibers formed a cluster that wrapped tightly around the lateral scp and extended across the external lateral (PBle) and external medial (PBme) parts. CCK immunoreactive-fibers occupied a large portion of the ventral lateral (PBlv) and PBle parts and moderately overlapped the territory occupied by the CGRP distribution. NT-immunoreactive fibers were observed in ventral and medial areas of the PB, as well as the troughs of the scp that bridge these two divisions. PS38(OT)-immunoreactive fibers were the most sparse of the fibers we observed, and were located predominantly in the lateral subnuclei. The atlas assignments shown here are a first step towards anatomically locating PB areas with dense expression of neuropeptides associated with feeding control, and will facilitate precise targeting of the anorexigenic pathways of the PB in future experiments.

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Poster

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Title: A topographically-defined hypothalamic-thalamic-striatopallidal connectional motif that supports hedonic processes

Authors: *K. NEGISHI[1,2], V. I. NAVARRO[1], L. SOTO ARZATE[1], J. M. GUERRA RUIZ[1], D. SOTELO[1], A. TOCCOLI[1], A. M. KHAN[1];
[1]Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX; [2]NIH/NIDA, Baltimore, MD

Abstract: Connectional topography is increasingly recognized as a widespread feature of forebrain organization. Corticostriatal projections, for instance, form a highly ordered patchwork of segregated and minimally overlapping fields. Significant progress has been made toward elucidating corticostriatal projection patterns; however, it is unclear how these are connected with downstream regions such as pallidum and hypothalamus. We have previously used a bottom-up strategy to reveal a topographically-defined hypothalamic-thalamic-striatal axis that includes the lateral hypothalamic area (LHA), paraventricular thalamic nucleus (PVT), and a dorsomedial part of the nucleus accumbens (dmACB) (Negishi *et al*., SfN Abstract, 2022). Here, we show that the ventral pallidum (VP; alternatively, the "substantia innominata") is part of this connectional motif. We co-injected *Phaseolus vulgaris* leucoagglutinin (PHAL) and cholera toxin B subunit (CTB) into the mPFC to examine input and output connections of VP simultaneously. Tracers were immunodetected and an adjacent Nissl-stained tissue series was used to delineate boundaries with the cytoarchitectonic definitions of Swanson (*Brain Maps 4.0*, 2018; *J. Comp. Neurol.*). Localized signal was mapped to atlas templates from *Brain Maps 4.0*. We show that CTB injections into VP exclusively labeled neurons in the dmACB. PHAL-labeled VP axons predominantly terminated in the LHA, confirming that VP is a critical node in this network. Next, we further elaborate VP connections throughout the forebrain. Strong CTB labeling was found in the LHA, PVT, subfornical organ, and the central nucleus of the amygdala. VP projections were found throughout the LHA, and were notably present in the PVT, lateral habenula, and ventral tegmental area. The present work suggests that the VP, receiving inputs from the dmACB, PVT, and LHA, is a central component of this network. The Berridge lab, using μ-opioid receptor agonists, has identified the dmACB and LHA as "hedonic hotspots," whereas the VP described here was identified as a "hedonic coldspot." Our work describes a circuit motif that joins brain regions relevant to hedonic and motivational processes, and juxtaposing our connectional maps with functional maps leads to novel questions for future experiments.

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Poster

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Title: High-spatial resolution mapping and three-dimensional architecture of the C1, C2, and C3 putative adrenergic neuronal groups and their neurites in the medulla of the rat brainstem: A light sheet microscopic study of PNMT immunoreactive structures

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Abstract: C1, C2, and C3 putative adrenergic neurons in the medulla are known for their role in autonomic control and their activation in response to hypoglycemia and hypoxia. Anatomical features of these putative adrenergic neurons and their neurites have been previously characterized in brainstem sections by immunostaining catecholamine synthesizing enzymes, especially phenylethanolamine *N*-methyltransferase (PNMT). However, their characterization at a mesoscopic scale has been limited to two-dimensional (2-D) medullary sections or three-dimensional (3-D) reconstructions of such sections with gaps. To our knowledge, the complete 3-D architecture of putative adrenergic neurons and their neurites in the medulla has not, to date, been visualized. To achieve this goal, we used tissue clearing combined with fluorescence immunohistochemistry and light sheet microscopy to produce volumetric renderings of the PNMT-immunostained brainstem. In tandem, we used atlas-based mapping methods on separate 2-D immunostained preparations of brainstem tissue to register the locations of PNMT-immunoreactive neurons to the open-access rat brain atlas of Swanson (*Brain Maps 4.0* (*BM4.0*), *J. Comp. Neurol.*, 2018), and to use these mappings as ground truth to register the 3-D dataset to *BM4.0*. Formaldehyde-fixed Sprague Dawley rat brainstems were protected using SHIELD hydrogel method and cleared through detergent based aqueous de-lipidation. These cleared rat brainstems were passively immunostained with PNMT primary and Alexa Fluor 647-tagged secondary antibodies, and scanned with a SmartSPIM light sheet microscope using a x3.6 objective lens. 3-D volume renders of the PNMT-positive neurons and their neurites were prepared using Imaris software. In addition, the spatial features of PNMT neurons and neurites from tissue sections were mapped onto *BM4.0* templates and their features compared to PNMT 3-D renders. In 3-D spatial exploration, we observed dense clusters of ventral C1 neurons and their interconnections with the dorsal C2 neurons on either side of the midline. These dorsal C2 neurons, in turn, were found to be interlinked by finely branched connections that crossed the midline of the brain, where the C3 neurons are, linking the two hemispheres in what appears to be a novel structural basis for coordinated and perhaps synchronized physiological control. In conclusion, complete volumetric renders allowed us to visualize and identify the mesoscopic-scale connectional network formed by the C1, C2, and C3 neuronal groups and their neurites. Future work could help determine the functional significance of these newly visualized network interactions.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

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Title: Pose tracking-based freezing detection reveals context-dependent features of fear response

Authors: *N. CANO ADAMUZ, R. DE LA VEGA RUIZ, C. REDONDO-ALAÑÓN, P. MENDEZ;
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Abstract: Freezing is a threat defensive response characterized by complete immobility, except for respiration. It is a robust measure of associative fear memory in rodent contextual fear conditioning, where learning occurs when aversive foot-shocks (unconditioned stimulus, US) are presented within a context (conditioned stimulus, CS). Freezing can be restricted to the conditioning context or extended to a similar neutral context. To understand the neuronal underpinnings of discrimination and generalization, it is essential to reliably detect freezing in different contexts while monitoring the activity of different neuronal populations.
The accuracy of automated freezing detection by video image-based detection software is challenged by differences in experimental contexts or when mice wear head-mounted hardware. We have implemented BehaviorDEPOT (Gabriel et al. 2022), which uses pose tracking data obtained with DeepLabCutTM (Mathis et al. 2018), to reliably detect freezing without interference from environmental factors. We validated this method's detection on our data based on the biological properties of freezing: 1) it appears in response to shocks and not in their absence (US-dependent), 2) is maintained when mice are re-exposed to the context 3 or 25 days after shock (long-term persistence), 3) is facilitated by previous context exploration (CS-dependent), 4) decreases with repeated context exposure (extinction).
Using this method, we characterized the freezing response in conditioning and neutral contexts. We show that freezing is differently regulated in each context and can be expressed with distinguishable features (incubation, number of episodes and duration). Manipulations of learning conditions such as shock intensity, number of presentations or shock zone (center or periphery) differentially affect these freezing features in the conditioning or the neutral context. In addition, we recorded with fiber photometry the activity of hippocampal regions (CA1 and DG) responsible for conveying contextual representations during freezing in both contexts. Preliminary analysis reveals changes in the activity of defined neuronal populations associated to

freezing behavior in both contexts.
In summary, we contributed to the biological validation of an automatic pose estimation-based freezing detection method in rodent fear conditioning experiments. We successfully implemented this method with fiber photometry recordings of neuronal activity. As a result, we demonstrate context dependent adaptation of freezing features to changes in learning conditions and describe the neuronal activity correlates of freezing in the hippocampus.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.02/LL15

Topic: G.01. Fear and Aversive Learning and Memory

Title: Study of Rodent Inequity aversion Revenge and the underlying Neural Mechanism

Authors: *Z. ZHANG, B. LIU, Z. WANG;
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Abstract: Inequity aversion is an instinctive emotion that is constant in the comparison of social values. In human, this emotion is termed envy. There is little work in rodent and on the underlying mechanism. The negative social emotions of individuals will also lead to the retaliatory behavior against specific individuals in the subsequent social behavior. Besides, the social influence of inequity stimulation remains largely unknown. We design a new paradigm, and use rat as model animal to investigate the inequity aversion mechanism. A two screens- two nose pokes decision making task is first designed to explore whether rats prefer equity reward or not. Rats make decision by choosing vertical stripe or horizonal stripe which represent equity or inequity respectively. We find that rat prefers equal reward instead of inequity, which is proved after stripes swapped. In addition, we examine the influence of social after going through enforced inequity treatment. Social time between equity partner and inequity partner shows no difference. Meanwhile, rats are more aggressive when faced with individuals whose rewards are better than their own. This revealed that rodent animals also have inequity aversion and inequity changed their neuroplasticity. Aggression of rats suffered inequity aversion displays different behaviors for distinct individuals. This finding indicate that inequity stimulation can modulate rats' social behavior. Furthermore, we examine the influence of hippocampus CA2 on inequity aversion and find inhibition of CA2 affects rat inequity aversion and the resulted revenge behavior. Taken together, we establish a new paradigm, demonstrate that rats prefer equity reward, and find that inequity aversion results in aggression behavior in a CA2-dependent manner.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

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Topic: G.01. Fear and Aversive Learning and Memory

Support: Neurophotonics Center at Boston University
NIH Transformative R01 Award
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Center for Systems Neuroscience, Boston University
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Title: Two-photon imaging of CA1 engram cells during memory retrieval

Authors: *A. MONASTERIO[1,2], S. COELLO[3], G. K. OCKER[4], B. B. SCOTT[3], S. RAMIREZ[3];
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Abstract: Memories are believed to be stored in the strengthened connectivity between distributed networks of neurons after learning. This biophysical memory trace is often referred to as an engram, provisionally defined as cells that are active during learning, reactivated during memory retrieval, and causally linked to behavioral expression of fear memory recall. Inducible genetic strategies have identified putative populations of engram cells in the hippocampus that express c-Fos during fear learning, and can drive the behavioral expression of memory. The current model for engram formation predicts that CA1 engram cells will become coactive with each other after learning due to strengthened synaptic inputs from upstream CA3 engram cells. To test this model in vivo, we developed a novel approach to record from engram cells across learning by combining the inducible tet-Tag strategy with large scale two-photon calcium imaging. We previously found that spontaneous activity of engram cells did not become more correlated after contextual fear learning. Therefore, we sought to see if memory retrieval may influence the real time dynamics of engram cells. Here we evaluated if CA1 engram neurons were more correlated with one another than non-engram cells during memory retrieval. We utilized the c-Fos-driven tet-Tag system to label CA1 engram neurons during auditory trace fear conditioning with a tone conditioned stimulus (CS). Two days later, we recorded from CA1

tagged engram and non-tagged cells during 10 trials of CS presentation to test for memory retrieval (n=3 mice, 580 cells). Surprisingly, engram cells were not more correlated during tone presentation relative to non-engram cells (2-Way RM ANOVA, p=0.12). This result replicates our finding from spontaneous activity of engram cells, however these findings are not in accordance with a simulated model of engram formation in which learning results in stronger synaptic weights between all engram cells. Two possibilities for this discrepancy may be that a small subset of tagged engram cells become coupled after learning or that engram cell reactivation is distributed in time. Further analyses to evaluate these possibilities is warranted in order to characterize the in vivo dynamics of engram cells during memory recall.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

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Chan Zuckerburg Foundation
Pew Foundation
Office of Naval Research
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NIH RO1DE030350

Title: Age differentially affects behavioral outcomes in a murine model of frontal lobe glioblastoma

Authors: *H. LEBLANC[1], E. RUESCH[1], X. VARELAS[2], S. RAMIREZ[1];
[1]Psychological and Brain Sci., Boston Univ., Boston, MA; [2]Biochem. and Cell Biol., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: Glioblastoma is the most common malignant central nervous system (CNS) tumor in adults. This disease not only has a poor survival prognosis, but also poses a severe burden on a patient's quality of life (QOL) due to the high rates of tumor-induced cognitive impairments,

which can be further exacerbated by age-associated cognitive decline. Due to the high patient mortality rates of glioblastoma, past research has focused on the development of survival-prolonging therapeutics, but few studies have investigated the accompanying cognitive and psychiatric symptoms that may improve QOL. To better address this gap, we developed a frontal lobe model of glioblastoma by introducing murine, high grade glioma cells into the medial prefrontal cortex of young (6-7 week old) and aged (85-86 week old) mice, and subjected them to a battery of behavioral tasks including the open field, tail suspension, social interaction, y-maze, contextual memory recall, and elevated zero maze, to test the effects of tumor burden and age on cognition and behavior. We additionally investigated whether the brain-region specific spread of each tumor could predict the behavioral phenotypes observed in tumor-bearing mice. We found a shared, increased "risk-taking" phenotype between young and aged mice in the elevated zero maze, but conversely found diverging results in the tail suspension test, with young mice struggling more and aged mice struggling less than their age-matched controls. These results emphasize the need to consider the demographics of a disease population when developing small animal models of pathology in systems and behavioral neuroscience. Our ongoing work seeks to 1) understand the neural underpinnings of the differential phenotypes expressed in young versus aged mice, and 2) target these mechanisms through optogenetic and pharmaceutical approaches to rescue the behavioral deficits observed. Together, our observations provide new insight into the mechanisms underlying glioblastoma-induced cognitive and behavior alterations.

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Poster

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Title: Hippocampal Engrams Flexibly Generate Behavioral Responses and Brain-wide Network States

Authors: *K. E. DORST[1], R. A. SENNE[2], A. DIEP[2], R. SUTHARD[4], A. R. DE BOER[5], E. A. RUESCH[3], M. BUZHARSKY[6], A. PYO[3], S. RAMIREZ[2];
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Abstract: Memory engrams are both necessary and sufficient to mediate behavioral outputs. Freezing behavior predominates when fear memory engrams are reactivated in constrained contexts, yet other experiments previously showed an avoidance behavioral phenotype when fear memory engrams were reactivated in spatially large arenas. How reactivation of a given fear memory engram engages the brain to produce various defensive behavioral strategies across contexts is relatively unclear. To address this, we first optogenetically reactivated a tagged fear memory engram in the dentate gyrus (DG) subregion of the hippocampus across three distinct contexts of various sizes. We found that there were differential amounts of within-animal light-induced freezing depending on the size of the context in which reactivation occurred: mice demonstrated robust light-induced freezing in the most spatially restricted of the three contexts but not in the largest. Next, we utilized graph theoretical analyses to identify brain-wide cFos co-activation patterns during engram reactivation across the smallest and largest contexts. We found that fear memory engram reactivation induced strong brain-wide correlation and regions spanning putative “fear” and “defense” systems were recruited as hub regions in the respective networks. Additionally, we show that fear memory engram reactivation and naturalistic fear memory retrieval are biologically degenerate (i.e., different configurations leading to the same behavioral outcome) network conditions to produce freezing behavior; there are shared hub regions across both experimental conditions, yet the mesoscale network composition had distinct structural features. By identifying and manipulating the circuits supporting memory function, as well as their corresponding brain-wide activity patterns, it is thereby possible to resolve systems-level biological mechanisms mediating memory’s capacity to modulate behavioral states.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

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Air Force Office of Scientific Research (FA9550-21-1-0310)
Center for Systems Neuroscience and Neurophotonics Center at Boston University

Title: Reactivation of a dorsal dentate gyrus engram differentially engages neurons and astrocytes in ventral hippocampus

Authors: *A. PYO[1], M. BUZHARSKY[3], R. SUTHARD[4], R. A. SENNE[2], A. DIEP[2], S. RAMIREZ[2];
[2]Boston Univ., [1]Boston Univ., Boston, MA; [3]Boston Univ. Undergraduate Program In Neurosci., Boston, MA; [4]Boston Univ., Boston Univ. Grad. Program For Neurosci., Boston, MA

Abstract: Though traditionally characterized as support cells, glial cells play an integral role in modulating circuit activity and cognition. Astrocytes, in particular, have recently been implicated in learning processes, including contextual fear conditioning, although their real-time involvement in fear encoding and maintenance is less understood, and even less is known about how they interface with neurons. Here we investigated how astrocytes and neurons in ventral CA1 (vCA1) in male mice respond during natural and artificial reactivation of a fear memory. To accomplish this, we combined activity-dependent labeling strategies and optogenetics in the dorsal dentate gyrus (dDG) with simultaneous in vivo fiber photometry to record the calcium dynamics of neurons and astrocytes in vCA1 during contextual fear conditioning, 'natural' recall, and 'artificial' optogenetic reactivation of a fear engram'. Mice received viral injections to express channelrhodopsin-2 (ChR2) or eYFP in the dDG and the genetically-encoded calcium indicators, jRGECO1a and GCaMP6f in vCA1 neurons and astrocytes, respectively.We first find that both neurons and astrocytes in vCA1 respond robustly to aversive foot shock during fear conditioning as well during fear memory recall. To further characterize astrocytic and neuronal activity across sessions, our ongoing work is evaluating event metrics, including peak height , full-width half max,, area under the curve,and frequency. Our preliminary results indicate that astrocytes alone exhibit experience-dependent changes in calcium event metrics during fear conditioning and natural recall. However, optogenetic stimulation impacts event metrics in neurons but not in astrocytes. Lastly, we will perform peri-event analysis to study calcium dynamics of astrocytes and neurons around the onset and offset of freezing bouts. Together, our results suggest that astrocytes and neurons are differentially engaged across fear learning, natural recall and artificial reactivation of a neutral or fear memory.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

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Title: Ketamine enhances performance on a perceptual evidence accumulation task

Authors: *C. DELGADO SALLENT, S. A. AHMED, A. RATNAKAR, A. KHAWAJA-LOPEZ, J. GOMEZ, S. RAMIREZ, B. B. SCOTT;
Boston Univ., Boston, MA

Abstract: The use of psychedelics have proven to be effective in treating psychiatric disorders, often producing a sustained effect after a single dose. While the therapeutic effects of these psychedelics have been related with their ability to promote structural and neural plasticity, these interventions produce brain-wide effects, and the neural and behavioral mechanisms underlying these effects are poorly understood. In this study we focus on ketamine to characterize its therapeutic properties by combining two different approaches: elucidating ketamine's effects on flexible decision-making parameters in mice, as well as studying the brain-wide mapping of drug-responsive populations by using activity-dependent gene expression. To find the effects of different doses of ketamine on decision-making, we trained mice on a free-response, pulse-based perceptual integration task. We find that after ketamine administration at medium-high doses (30-50 mg/kg) mice slowed their response times (RT) and increased accuracy in the task. Subsequently, we fitted a drift diffusion model (DDM) that suggested that the slower decision time induced by medium-high dose ketamine administration is due to an increased boundary separation and non-decision time. RTs were well fit by the DDM, and parameter fits suggested that mice use a multi-flash accumulation strategy. To further characterize which brain regions are activated by ketamine administration (30 mg/kg), we combined whole-brain immuno-staining of the activity-dependent immediate early gene, c-fos, with the theoretical framework of graph theory. By measuring the difference in cfos expression between ketamine and saline and also applying topological measures of centrality to correlation networks we observed changes in several regions, particularly in specific thalamic areas, that we identify as key regions in our networks (hubs). To address the causal role of these network hubs our ongoing work plans to do targeted reactivation of cell populations active during ketamine administration to recapitulate ketamine's effects. Taken together, our results indicate that subanesthetic doses of ketamine improves perceptual evidence accumulation by raising the decision threshold and allowing the integration of more evidence before the decision.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.08/LL21

Topic: G.01. Fear and Aversive Learning and Memory

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Center for Systems Neuroscience and Neurophotonics Center at Boston University

Title: A hippocampal astrocyte ensemble is activated during fear learning and memory.

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Abstract: The dorsal CA1 (dCA1) subregion of the mammalian hippocampus has been well studied in the context of episodic memory, spatial coding, and navigation. Most published research on dCA1 focuses nearly entirely on its neuronal populations, but recent work has begun studying the glial counterparts present throughout dCA1-namely astrocytes. Astrocytes, once thought as supporting cells of the brain, have now been widely implicated as important choreographers in neuronal communication, releasing gliotransmitters, supporting metabolic needs during sustained neurotransmission, pruning synapses, and affecting synaptic plasticity. Recent studies have shown that the perturbation of dCA1 astrocyte populations has the capacity to both enhance and weaken fear memory at remote and recent timepoints and that these populations can even encode reward locations (Doron et. al., 2022; Adamsky et. al., 2018; Kol et. al., 2020). However, there has not been a systematic characterization of how these cells may be implicated in fear memory processing in the region and how stable these populations are across timepoints. To address this, we injected AAV-GfaABC1D-cyto-GCaMP6f-SV40 into the dCA1 of the hippocampus of male C57BL/6J mice to selectively express a genetically-encoded calcium indicator in astrocytes. We paired this with the implantation of a gradient-index (GRIN) lens to record freely-moving one-photon calcium imaging across a standard contextual fear

memory paradigm. We find that there is a small but stable population of hippocampal astrocytes that encode various aspects of the fear memory and that there are unique physiological signatures across this population. We further report that mice re-exposed to the original fear context show robust markers of memory recall in these populations compared to a group exploring a novel context. Our results demonstrate that astrocytes play a crucial, and equally important, role in learning and memory and that their physiological dynamics are intimately tied to the behavioral expression of fear.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.09/LL22

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH DP5
Ludwig Foundation
HHMI Gilliam

Title: The role of positive and negative engrams in memory-guided decision making

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Abstract: The ability to make flexible memory-guided decisions is fundamental to our daily lives. Such decision-making often requires a strategically balance between motivational drives including the pursuit of reward and avoidance of danger, which become impaired in pathological states such as addiction and anxiety disorders. Here, we aim to understand the underlying mechanisms that support such flexibility during memory-guided decision-making. To this end, we developed a novel decision-making task that allows animals to strategically combine the drive to approach a reward and avoid a footshock without compromising either goal. During training, mice learn that a 30s light cue indicates the availability of reward at a nose port (i.e. sucrose water), and a 30s auditory cue predicts the onset of a footshock which they can avoid by stepping onto a platform. After animals learn the reward and punishment contingencies, the light and auditory cues are delivered at the same time, creating a conflict between reward-seeking and punishment avoidance. Over the course of 7 days, we find that mice initially utilize unique sex-specific strategies that then converge over 7 days on the same resolution to this conflict. Initially, female mice are more risk-taking and opt to get the maximal reward at the expense of

footshocks. However, by day 7 all mice learn to balance both drives: seek reward early during the simultaneous cue presentations while then stepping on the platform towards the end of the cue presentations, thus avoiding the footshock without omitting reward seeking. To mechanistically study the brain regions recruited during this flexible decision-making process, we combined whole-brain inmuno-staining of the activity-dependent immediate early gene cFos with the theoretical framework of graph theory. By applying topological measures of centrality to correlation networks created from cFos expression we identified several regions (i.e. Hubs) in our networks, with the prelimbic cortex (PL) playing a key role. We next utilized population calcium imaging to record real-time calcium dynamics of both PL during memory guided decision-making and found the PL bidirectionally encodes avoidance and reward seeking behaviors. Additionally, we found that the PL differentially encodes trials in which memories were incorrectly balanced to maximize rewards and minimize punishment. Our ongoing experiments aim to chemogenetically perturb valance specific engrams to bias decision-making. Overall, our findings suggest the PL may play a critical role in arbitrating positive and negative memories during memory-guided decision making.

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Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR288.10/LL23

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant R01 MH099073 (J.J.K.)
NIH Grant R21 AG067008-01 (E.J.K.)

Title: The role of the ventral hippocampus in navigating predatory environments

Authors: ***X. LI**[1], M.-S. KONG[2], E. J. KIM[1], B. P. SCHUESSLER[4,5], J. J. KIM[1,3]; [1]Psychology, Univ. of Washington, Seattle, Seattle, WA; [2]Dept. of Psychiatry and Behavioral Sci., [3]Program in Neurosci., Univ. of Washington, Seattle, WA; [4]VA Northwest Geriatric Research, Educ. and Clin. Ctr., [5]VA Northwest Mental Illness Research, Educ. and Clin. Ctr., VA Puget Sound Hlth. Care Syst., Seattle, WA

Abstract: The hippocampus is posited to show functional segregation along its longitudinal axis, with the dorsal hippocampus (dHPC) and ventral hippocampus (vHPC) playing pivotal roles in cognitive and emotional processes, respectively (Fanselow and Dong, 2010; Strange et al., 2014). This view is corroborated by evidence demonstrating that selective lesions or inactivation of the dHPC impairs fear conditioning by affecting contextual and trace cues (e.g., Phillips and LeDoux, 1992; Chowdhury et al., 2005), whereas selective lesions/inactivation of the vHPC lead to generalized impairment in fear and anxiety by impacting innate or unconditioned fear

processes (e.g., Kjelstrup et al., 2002; Bannerman et al., 2003). Through an ecologically relevant "approach food-avoid predator" (AFAP) paradigm (Choi and Kim, 2010), we previously discovered that dHPC neurons also contribute to distance-gradient risky foraging decision-making (Kim et al, 2015). The present study investigated the function of vHPC using the same AFAP task. Long-Evans rats underwent either vHPC or sham lesion surgery and maintained 85% normal body weight to motivate food-seeking behavior during the baseline phase. On the test day, animals underwent pre-predator trials followed by predator exposure trials, with food pellets placed at various distances to the predatory robot. The findings suggest that animals with vHPC lesions showed diminished fear responses to the robot, evidenced by shorter latency to acquire pellets, including when placed in close proximity to the robot. Sham animals were comparably less successful at acquiring pellets and exhibited longer latencies. A subsequent study in C57BL mice also revealed heightened c-Fos expression in the CA1 region of the vHPC following predatory exposure in an AFAP task, compared to the foraging-only control group. Collectively, these results indicate that vHPC cells respond to predatory threats, thereby underscoring the potential significance of vHPC in natural fear behavior. Our ongoing research is employing electrophysiological techniques to study the activity of vHPC neurons in rats performing risky foraging tasks, aiming to deepen our understanding of this critical region.

Disclosures: X. Li: None. **M. Kong:** None. **E.J. Kim:** None. **B.P. Schuessler:** None. **J.J. Kim:** None.

Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

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Title: Spatiotemporal multi-omics analysis of the hippocampal-amygdala circuit during contextual fear memory consolidation

Authors: *X. XU[1,2], Y. LIN[1,2], M. LIU[1,2], T. JAROME[3], H. XIE[1,2,4];
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Abstract: The consolidation of contextual fear memories requires the crosstalk among multiple brain regions, including the hippocampus and amygdala. Despite the advance in single cell transcriptomic techniques, tracing the dynamic gene expression across the hippocampal-amygdala circuit remains challenging. Here we integrated high resolution spatial transcriptomics with single nuclei multi-omics techniques to systematically investigate the spatiotemporally transcriptional programs across the hippocampal-amygdala circuit during the encoding and retrieval of contextual fear memory. It reveals brain region-specific gene expression changes during memory consolidation, especially in the subregions of hippocampus and amygdala. Furthermore, it showed cell-type specific epigenetic and transcriptional changes during the contextual fear memory consolidation. Our data provides new insight into the spatiotemporal and cell-type specific transcriptional programs during memory consolidation.

Disclosures: **X. Xu:** A. Employment/Salary (full or part-time):; Virginia Polytechnic Institute and State University. **Y. Lin:** A. Employment/Salary (full or part-time):; Virginia Polytechnic Institute and State University. **M. Liu:** A. Employment/Salary (full or part-time):; Virginia Polytechnic Institute and State University. **T. Jarome:** A. Employment/Salary (full or part-time):; Virginia Polytechnic Institute and State University. **H. Xie:** A. Employment/Salary (full or part-time):; Virginia Polytechnic Institute and State University.

Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.12/LL25

Topic: G.01. Fear and Aversive Learning and Memory

Support: R01 MH117426-01A1

Title: Effects of stress on formation and retrieval of hippocampal ensemble representations of contextual fear memory

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Abstract: The stress-enhanced fear learning (SEFL) model recapitulates components of PTSD, such as stress-induced sensitization of fear learning. The SEFL procedure uses components of Pavlovian fear conditioning but generates a marked stress-sensitized fear response. The SEFL procedure entails exposing mice to footshock stress in context A (10 shocks, 2 s, 1 mA). On a separate day, mice receive a single shock at a lower intensity (0.75mA), in another context. 24 hrs later, mice are placed in context B and tested for fear recall. Stressed mice show higher freezing in context B. We used the SEFL model to investigate effects of stress on fear memory encoding and retrieval in the dentate gyrus and CA1. Fear memory representations in the hippocampus were investigated using activity-dependent neuronal tagging with FosTRAP/Ai6

mice, whereby cells activated during a discrete event are labeled using the IEG promoter elements to initiate the expression of a tag (zsGreen) following injection of tamoxifen. Prior research shows tagged fear engram cells are reactivated during fear memory recall, and the degree of reactivation of fear engram cells is correlated with the percentage of freezing during fear memory recall. We used the FosTRAP2/Ai6 system to investigate how prior stress exposure affects formation and reactivation of contextual fear ensembles. Male and female FosTRAP2/Ai6 mice received shock stress (or exposure to the context) on day 1. From days 2-5, mice were re-exposed to the stress context (context A) to extinguish fear of the stress context and reduce generalization to context B. On day 6, mice received conditioning in context B and immediately after received an injection of 4-OHT (55mg/kg). On day 7, mice were tested for fear recall and were perfused 90 minutes after. We examined the number of 1) zsGreen+ fear engram cells, 2) recall-activated cells (Fos+cells), and 3) fear engram cells reactivated during recall (Fos+ and zsGreen+) in the dentate gyrus and CA1. Our preliminary results show that prior stress increases the number of fear engram cells in the dorsal dentate gyrus, but does not change the number of activated cells (Fos+) during recall, the total number of reactivated engram cells (Fos+ and zsGreen+ cells/mm2), or the percent of reactivated cells. Thus, stress enhances the encoding of contextual fear, but does not affect the reactivation of a contextual fear memory. Ongoing experiments will determine if stress affects the number of cells in the fear engram, fear recall, or co-activated cells in CA1 and will examine differentiation along the dorsal-ventral axis. These studies are expected to reveal novel mechanisms for the stress-induced sensitization of fear learning.

Disclosures: D. Paredes: None. **M.R. Drew:** None.

Poster

PSTR288. Neural Circuits of Fear and Aversive Processing: Hippocampal Circuits

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Program #/Poster #: PSTR288.13/LL26

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant MH 117426-01A1

Title: Role of the paraventricular thalamus in stress-induced fear sensitization

Authors: *K. NISHIMURA[1,2], D. PAREDES[2], N. A. NOCERA[2], M. R. DREW[2];
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Abstract: Stressful experiences can lead to long-lasting alterations in emotional fear responses. Excessive and disproportionate fear that extends beyond contexts or situations related to the traumatic event may resemble symptoms of hyperarousal, commonly observed in individuals with post-traumatic stress disorder. Although the neural circuitry underlying Pavlovian conditioned fear to a discrete stimulus has been well studied, the circuits recruited by a single stressful event to ubiquitously sensitize fear remain poorly understood. In the current study, we

characterized the behavioral and neural mechanisms of stress-induced fear sensitization using a novel mouse model. Mice were assigned to a “Stress” group that received four 1-mA foot shocks or a “No Stress” group that received equivalent context exposure. Following 24 hours, animals exposed to stress exhibit a persistent phenotype of fear sensitization characterized by (1) decreased exploration in the open field, (2) potentiated unconditioned fear of a novel tone, and (3) stress-enhanced fear learning (SEFL) in a novel context. Stress-induced fear sensitization to unconditioned tone and SEFL are resistant to extinction training in the stress context, indicating that non-associative learning facilitates this process. Next, c-fos analysis was performed to identify candidate brain regions that mediate fear sensitization. We identified several brain regions that were hyperactive in stressed animals including the paraventricular thalamus, dorsolateral periaqueductal gray, and the lateral parabrachial nucleus. Using fiber photometry, we confirm *in vivo* that stress leads to potentiated activity in the paraventricular thalamus in response to aversive or threatening stimuli. Finally, we used chemogenetic manipulations to show that the paraventricular thalamus is both necessary and sufficient for fear sensitization to unconditioned tone. Interestingly, silencing or activating the paraventricular thalamus had no effect on associative context fear conditioning. Overall, the data indicate that fear sensitization is not contingent on the initial associative fear memory and is likely acquired and maintained through dissociable neural mechanisms.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.01/LL27

Topic: G.02. Reward and Appetitive Learning and Memory

Support: OD P51 011132

Title: The ventral hippocampus plays a critical role in habitual behaviors

Authors: *J. BHALERAO, E. SEO, A. G. ALLEN, S. L. GOURLEY;
Emory Univ., Atlanta, GA

Abstract: Habits are familiar actions that have been repeatedly performed and rewarded in the past, such that they manifest repeatedly and are triggered by cues in the environment rather than specific outcomes. While habitual responses are an important component of our behavioral repertoire, overreliance on them can lead to inflexible and maladaptive decision-making. The ventral hippocampus (vHC) appears to control the development of habitual behaviors, but its involvement in the *expression* of habits has largely not been explored. We used projection-specific G_q-coupled designer receptors exclusively activated by designer drugs (DREADDs) to stimulate vHC-to-central nucleus of the amygdala (CeA) projections in mice tested for their sensitivity to changes in action-outcome contingency. Stimulation of vHC-CeA projections

induced the expression of habits - that is, behaviors that were insensitive to action contingency. Next, we used schedules of reinforcement that induce habitual or non-habitual behaviors to examine neurobiological adaptations in the vHC to habit formation and execution. In conclusion, vHC-CeA connections exert control over the expression of habitual behaviors. Future experiments will reveal hippocampal-amygdalo-striatal connectivity by which familiar habits are executed, as well as substrates of vHC plasticity underlying habitual and non-habitual reward-seeking. These outcomes will serve as a platform by which to investigate vHC hyper-activity in disorders associated with persistent habitual behaviors, such as autism spectrum disorders.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.02/LL28

Topic: G.02. Reward and Appetitive Learning and Memory

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Title: Emotional association enhances perceptual memory through amygdalo-cortical inputs during NREM sleep

Authors: *Y. SAITO[1,2], Y. OSAKO[1,3], M. ODAGAWA[1], Y. OISI[1], C. MATSUBARA[1], S. KATO[4], K. KOBAYASHI[4], M. MORITA[2], J. P. JOHANSEN[1], M. MURAYAMA[1];
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Abstract: Long-lasting memories of perceived information associated with emotionally arousing experiences (e.g., sexual, threatening) are critical for animal reproduction and survival. Emotional arousal is thought to enhance the consolidation of associated memories by activating the basolateral amygdala (BLA) and its projections to memory-storing regions. Although the importance of both rapid eye movement (REM) and non-REM (NREM) sleep-state specific BLA activity for emotional memory processing has been proposed, how and when the BLA interacts with other brain regions to enhance memory consolidation remains unclear. Here, by adding emotional information to a tactile perceptual recognition task that relies on a top-down circuit from the secondary motor cortex (M2) to the primary somatosensory cortex (S1), we dissociated the perceptual memory consolidation and memory modulation. Anatomical experiments showed

that the BLA projects to M2, but not to S1, and may influence the top-down M2-S1 circuit underlying perceptual memory consolidation. Chemogenetic inactivation of the BLA-M2 circuit demonstrated that the BLA not only associates emotional information with perceptual information, but also enhances perceptual memory consolidation via BLA-M2 projections. Electrophysiological recordings revealed that emotional association increased the reactivation of coordinated activity across the BLA-M2-S1 during NREM sleep, but not during REM sleep. Notably, this inter-regionally coordinated reactivation during NREM sleep was entrained to the BLA high-frequency oscillations in the emotional condition, suggesting that the BLA triggers inter-regional interaction. Optogenetic silencing of BLA terminals in the frontal cortex during NREM sleep, but not REM sleep, disrupted the enhanced retention of the perceptual memory, but not the association itself or the emotional component of associative memory. These findings indicate that increased interregional reactivation via BLA-cortical inputs during NREM sleep is the neural basis for memory enhancement by emotional arousal.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.03/MM1

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA Intramural Funds ZIA DA000069

Title: Examining the Role of Zn^{2+}-Releasing Neurons and Circuitry in Reward Related Regions

Authors: *F. P. CURRY, O. SOLÍS CASTREJÓN, M. MICHAELIDES;
Biobehavioral Imaging and Mol. Neuropsychopharm. Br., NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD

Abstract: Vesicular or synaptic zinc (Zn^{2+}) is an essential element necessary for maintaining neurophysiological homeostasis. Previous literature has established that the striatum receives dense innervation from Zn^{2+}-releasing glutamatergic neurons. In addition, synaptic Zn^{2+} plays a critical role in modulating striatal dopamine neurotransmission, influencing cocaine's effect on synaptic transmission. However, little is known about the molecular profile of Zn^{2+}-releasing neurons in circuits related to reward and the proportion of Zn^{2+}-releasing neurons that project to the striatum. To characterize Zn^{2+}-releasing neurons, we performed RNAscope in situ hybridization (ISH) in reward related circuits (prefrontal cortex, orbitofrontal cortex, paraventricular thalamus, hippocampus, and amygdala) of male and female mice. We utilized mRNA probes that indicate the presence of glutamatergic neurons as well as probes that indicate the presence of GABAergic neurons (including parvalbumin, somatostatin, and VIP subtypes).

We then quantified the colocalization of these probes with ZnT3 mRNA, which represents Zn^{2+}-releasing neurons in our regions of interest. Through this colocalization analysis, we confirmed that there are notable numbers of Zn^{2+}-releasing neurons in these regions. Additionally, we discovered that Zn^{2+}-releasing neurons in these regions are primarily glutamatergic but also include a subset of GABAergic neurons. We also observed differences in the proportions of Zn^{2+}-releasing glutamatergic neurons between male and female mice, with female mice showing higher proportions of these neurons in the prefrontal cortex. Along with the molecular profile, we performed combined immunohistochemistry and RNAscope ISH using Fluorogold to identify the Zn^{2+} circuits projecting to the nucleus accumbens and dorsal striatum. Our preliminary results showed that there are Zn^{2+}-releasing projections from the previously stated regions of interest to the nucleus accumbens and the dorsal striatum, which suggests a role for synaptic Zn^{2+} in reward. Future work will use fiber photometry in awake mice during reward-related behaviors to study Zn^{2+} dynamics in the striatum.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.04/MM2

Topic: G.02. Reward and Appetitive Learning and Memory

Support: P50 MH096889

Title: Sex dependent influence of early life adversity on reward circuits

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Abstract: Rationale: Early life adversity (ELA) involves exposure to adverse, negative experiences during infancy and childhood. Humans with a history of ELA have an increased risk for depression, anxiety, and PTSD in a sex-dependent manner: women are more likely to be diagnosed with anxiety and depression than men. Disruptions in reward circuits may cause these disorders, but it is unknown how ELA directly impacts the development of this circuitry. Similarly to the human condition, ELA has contrasting effects on rodent male and female reward-seeking behaviors: adult ELA males are ‘anhedonic’ whereas females exhibit augmented reward behaviors. We identified a novel corticotropin-releasing hormone (CRH) expressing

GABA-ergic projection connecting the basolateral amygdala (BLA) to the nucleus accumbens (NAc) to be responsible for reduced reward-seeking behavior in adult male mice that experienced ELA. However, the functions of this projection in female mice are unknown. Here we investigate the role of this pathway in female mice and potential structural differences between males and females. Methods: We used chemogenetic approaches to investigate the function of the CRH/GABA BLA-NAc pathway in reward-seeking behavior in female mice. CRH-IRES-Cre mice raised in either control conditions or ELA conditions were injected bilaterally into the BLA with an excitatory or inhibitory Cre-dependent DREADD, followed by delivery of clozapine N-oxide (CNO) or vehicle through direct infusion into the medial shell NAc. Separately, mice were injected bilaterally into the BLA with a Cre-dependent channelrhodopsin. Using brain-clearing techniques, we mapped CRH projections from the BLA to NAc to determine whether the projection projects to different areas of the NAc or target cells in female and male mice. Results: Excitation of the CRH/GABA BLA-NAc projection did not influence reward behaviors in either control or ELA female mice, suggesting that the pathway is not involved in mediating reward behavior in females. Studies inhibiting the projection in female mice are ongoing. Studies mapping this projection in males and females are in progress to pinpoint structural differences. Conclusions: We characterized a novel CRH/GABA BLA-NAc pathway mediating the effects of ELA on reward circuits in male mice and are striving to determine if the neuroanatomy and cell-type specificity of the projection is the same in females. Investigating this projection will give us a deeper understanding of intrinsic sex differences in the organization of the reward circuitry and the effects of ELA on reward behaviors that underlie many mood disorders.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Topic: G.02. Reward and Appetitive Learning and Memory

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Harvard Brain Science Initiative Postdoc Pioneers Grant

Title: Glutamate inputs send prediction error of reward but not negative value of aversive stimuli to dopamine neurons

Authors: *R. AMO, N. UCHIDA, M. WATABE-UCHIDA;
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Abstract: Midbrain dopamine neurons are thought to signal reward prediction errors (RPEs). Typical circuit models assume that isolated components of RPE computation such as reward and expectation are carried by glutamate and GABA inputs to dopamine neurons, although the exact mechanisms remain poorly understood. Here we used a genetically-encoded glutamate sensor (SF-iGluSnFR) to examine the pattern of glutamate inputs to dopamine neurons in the ventral tegmental area. We found that glutamate input responses to reward-predicting cues positively correlated with associated value, while responses to water reward negatively correlated with reward expectation. Omission of expected reward reduced glutamate input activity below baseline. Thus, glutamate inputs to dopamine neurons convey a fully-formed RPE signal, in contrast to leading RPE models. Further, when animals were trained with sequential conditioning in which serial cues (distal, then proximal) signal reward probability, both dopamine and glutamate input activities at a rewarding proximal cue were suppressed when preceded by a distal cue predicting reward. The expectation-dependent suppression of cue responses supports a specific form of RPE, temporal difference (TD) error, in both dopamine neurons and their glutamate inputs. Notably, glutamate inputs were excited by aversive stimuli, while dopamine neurons were inhibited by the same aversive stimuli, suggesting competition between glutamate and GABA inputs. Opioid analgesics caused dopamine responses to aversive stimuli to become positive rather than negative, but did not change excitatory responses of glutamate inputs, and thus likely biased competition between glutamate and GABA inputs. Our findings uncover previously unknown mechanisms underlying RPE computations: dopamine responses are shaped by both synergistic and competitive interactions between glutamate and GABA inputs, with the nature of the interaction (synergistic or competitive) dependent on stimulus valence.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.06/MM4

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NSERC
Ludmer Centre

Title: Nucleus accumbens glutamatergic afferents integrate outcomes in reward-learning

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Abstract: The ability to integrate information about reward over time is essential to reward learning. While the role of dopaminergic inputs to the nucleus accumbens (NAc) is widely studied, the role of accumbens glutamatergic afferents in reward learning is relatively unexplored. Using in vivo fiber photometry, we simultaneously record population-level activity of medial prefrontal cortex (mPFC) and ventral hippocampus (vHIP) projections to NAc in male and female adult mice performing a two-armed bandit task. We find that both mPFC and vHIP projections to NAc dynamically encode information outcome history, with subtle sex- and pathway-way specific differences. mPFC-NAc tracks the recent history of reward and loss in females but only the recent history of loss in males. In contrast, vHIP-NAc preferentially encodes recent history of loss, but not reward. To determine the precise information encoded in these neural signals, we manipulated task design to systematically degrade behavioral requirements. This revealed that outcome history is tracked preferentially when linking a behavioral response with an outcome. However, when action-outcome pairing is not relevant, mPFC-NAc encodes immediate outcomes but not outcome history and vHIP-NAc fails to encode any outcome information. Together, these findings establish that mPFC-NAc and vHIP-NAc integrate outcomes over time when outcomes are contingent upon behavior and reveal a neural mechanism for the propagation of reward-associated information over time.

Disclosures: E.S. Iyer: None. **J. Muir:** None. **R.C. Bagot:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.07/MM5

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Involvement of the ventral tegmental area to central amygdala pathway in food consumption behavior

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Abstract: Mesolimbic dopamine is known to be critically involved in food related reward processing and learning. The central amygdala (CeA) in the other hand, is one of the critical brain regions playing a significant role in various behavioral responses such as reward processing, energy valence and feeding behavior. Numerous studies describe the involvement of dopamine signaling and central amygdala in the associative learning, including fear and extinction learning, but little is now about how dopamine regulate the central amygdala during feeding behavior. In this study we evaluate the ventral tegmental area (VTA) → CeA pathway during food consumption. Using fiber photometry and a genetically encode calcium sensor (GCamP6) were able to monitor dopamine axon in the CeA in head fixe mice during Pavlovian feeding behavior. Interestingly we were able to demonstrate that dopamine signal was strongly

modulated by food consumption, but also that the same projection also responds to negative input. Our finding demonstrates that dopaminergic neurons projecting to the CeA might not encode reward prediction error but should be more involved in salience coding.

Disclosures: **D. Kerspern:** None. **G. Gabrielson:** None. **J. Isaac:** None. **A. Lutas:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.08/MM6

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Interrogating ventral pallidal circuits as a therapeutic target for diet-induced obesity

Authors: *J. WANG[1], T. THOMPSON[1,3], A. V. KRAVITZ[2];
[2]Psychiatry, [1]Washington Univ. in St. Louis, St. Louis, MO; [3]Psychology, The Col. of Wooster, Wooster, OH

Abstract: People with obesity experience physiological, neural, and behavioral changes resulting in decreases in metabolic rate and increases in appetite, making weight-loss extremely challenging. As to why obesity pathology is persistent, our overarching hypothesis is that obesity strengthens feeding neural circuits driving the continued consumption of palatable foods in excess of caloric requirement. To inform novel therapies for producing robust weight loss, it is critical to understand the mechanism for how these foods alter neural circuits involved in initiating and sustaining pathological overeating behavior. While many brain areas have been implicated in appetite control, this research focuses on the ventral pallidum (VP), a brain region involved in reward processing and incentive motivation. However, the potential of manipulating VP activity to suppress or reverse excessive body weight remains unknown. To test this, we used ad libitum high fat diet (HFD) access as a mouse model of diet-induced obesity. After 6 weeks, animals received bilateral injections of quinolinic acid into the VP, producing robust excitotoxic lesioning of neurons. We found that VP lesioning in both males and females promotes a lean phenotype characterized by reduced HFD consumption and enhanced energy expenditure, resulting in complete reversal of HFD-induced weight gain. Additionally, to test whether directly inhibiting the VP neural activity modulates high-fat consumption, we employed an optogenetic strategy through viral expression of the inhibitory opsin Arch3.0 in VP^{GABA} neurons. Based on previous research demonstrating that pharmacological manipulation of VP^{GABA} neurons modulated fat-specific intake, we reasoned that optogenetic inhibition of VP^{GABA} neurons would reduce consummatory behavior for fat-enriched rewards. Using a head-fixed liquid fat consumption task, we employed closed loop optogenetic stimulation on VP^{GABA} neurons to determine whether optogenetic inhibition of GABAergic cell bodies in the VP could produce similar effects seen in QA-lesioned mice. We performed licking microstructure analysis to evaluate the palatability of various fat-enriched liquid rewards and assessed whether changes and licking behavior were observed with and without optogenetic stimulation.

Disclosures: **J. Wang:** None. **T. Thompson:** None. **A.V. Kravitz:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.09/MM7

Topic: G.02. Reward and Appetitive Learning and Memory

Title: The Role of Insulin Receptors on Striatal Cholinergic Interneurons in Weight Gain

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Abstract: Although prior literature once limited insulin to the peripheral nervous system, research on insulin receptors (IRs) in the brain is evolving. IRs are found throughout the brain, including the striatum, a brain region implicated in feeding behavior, motivation, and reward. There are 4 main cell types in the striatum that contain insulin receptors: cholinergic interneurons (CIN), medium spiny neurons, glial cells, and astrocytes. Although the presence of striatal IRs suggest the presence of insulin, the role of these IRs on CIN in the striatum remains under-researched. Because the striatum plays an integral role in food intake, we aimed to explore the function of IRs in maintaining body weight. To narrow our search, we focus on the IRs on CIN. We generated a transgenic mouse with a selective knockdown of IRs on the CIN (IR-KO) and littermate controls. To elucidate the role of striatal IRs in weight gain, body weights of 5-week-old male and female IR-KO (n = 10) and control (n = 9) mice were taken weekly for 28 weeks. IR-KO mice gained more weight compared to littermate controls. IR-KO mice also consumed more palatable food as evidenced by a sugar pellet consumption paradigm. Peripheral metabolic function is conserved in the IR-KO mice as there were no significant differences in basal glucose levels, and glucose and insulin tolerance between IR-KO and control mice. Performance in the novel object recognition test was not significantly different between IR-KO and control mice indicating that cognitive performance was not impaired. Collectively, the results highlight that this specific population of IRs on CIN in the striatum play a notable role in both feeding behavior and weight gain. The lack of untargeted peripheral changes support the importance of IRs in the central nervous system. Future considerations include testing for locomotor differences between IR-KO and littermate control mice. The function of striatal IRs are imperative to study as they may link obesity to certain genetic factors in a time where obesity is an epidemic.

Disclosures: **M. Mahboob:** None. **M. Bocarsly:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: R00DA042934 (NIA/NIDA) to EAW

Title: Alzheimer'S disease transgenic rats show altered prelimbic neurophysiological signatures to reward predictive cues following a change in expected outcome

Authors: T. J. SLOAND, B. DUNHAM, S. CORAGGIO, M. NIEDRINGHAUS, ***E. WEST**; Rowan Univ. SOM, Stratford, NJ

Abstract: Deficits in the ability to flexibly shift behavior in response to changing outcomes can have devastating consequences for one's decision-making. In Alzheimer's disease (AD) patients, behavioral deficits often precede the accumulation of neuropathological markers (Aβ plaques and tau pathology) and severe dementia. The Tg-F344-AD rat model expresses mutant amyloid precursor protein, overexpresses presenilin-1, and exhibits age-dependent AD pathology. At 6 months of age, AD rats show deficits in flexible behavior. Prelimbic cortex (PrL) neural encoding of reward-predictive cues during learning is both necessary for and predictive of a rat's ability to flexibly shift behavior following outcome devaluation. Here, we investigated if AD rats show aberrant PrL neural activity and/or behavioral responding to reward predictive cues following outcome devaluation. 6-month-old male and female AD rats (n=7) and wild-type littermate controls (n=8) were presented with two distinct cues as conditioned stimuli (CS+) predicting distinct rewards. A conditioned taste aversion to one reward was induced by pairing the reward with lithium chloride. Rats were then tested on the same Pavlovian task to evaluate the ability to avoid the devalued CS+. WT rats spent less time attending and had fewer phasic PrL neurons to the devalued (D) CS+ compared to the non-devalued (ND) CS+. In comparison, AD rats attended to both CS+ equally, and the number of phasic PrL neurons did not differ to either CS+. Phasic PrL neurons in WT rats were primarily inhibited to both CS+, especially to the D cue, while phasic PrL neurons in AD rats were primarily excited to both CS+ regardless of devaluation status. Further analyses revealed that in WT rats, more excited PrL neurons selectively respond to the ND cue and fewer neurons respond to both cues (ND: 80%, both: 20%, D:0%) suggesting that the PrL disengages during the D cue in WT rats. In contrast, AD rats do not show the same devaluation-induced dynamic PrL encoding, as AD rats show a similar number of excited PrL neurons that selectively respond to ND and D cues equally (ND: 38%, both: 31%, D: 31%). This hyperactive PrL encoding of the CS+ in AD rats is likely contributing to their impaired ability to shift behavior away from the D CS+. Additionally, AD rats' local field potential (LFP) power to both CS+ was significantly less than WT rats', particularly in the 8-12 Hz range. This study contributes to the overall understanding of neurobiological disruptions in AD before the neuropathology accumulation to inform future studies for potential therapeutic interventions such as noninvasive brain stimulation.

Disclosures: T.J. Sloand: None. **B. Dunham:** None. **S. Coraggio:** None. **M. Niedringhaus:** None. **E. West:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.11/MM9

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Functional mapping of reward responses in the lateral septum along the dorsoventral axis

Authors: *S. KARKARE[1], J. ISAAC[1], M. MALAVIKA[2];
[2]Emory Univ., [1]Emory Univ., Atlanta, GA

Abstract: The lateral septum (LS) has been implicated in a wide range of behaviors, including aggression, reward-related behaviors, kin recognition, sexual behaviors, and social memory. While the specific role of the LS in mediating such a variety of behaviors is unclear, its anatomical heterogeneity has been suggested as a putative contributor to its functional diversity. Discrete LS compartments have been identified by specific properties, such as connectivity with the hippocampus and hypothalamus, as well as the differential expression of receptors and neuropeptides. Recent evidence suggests that subregions of the LS might play a role in modulating both approach and avoidance behaviors. In particular, there appears to be functional clustering of neurons along the dorsoventral (DV) axis within the LS, with approach behaviors modulated by neurons localized to the dorsal subdivision of the LS, while avoidance behaviors are mediated by neurons in the ventral LS. However, it is unclear how reward responses are organized along the DV axis of the LS. In this study, we performed monosynaptic rabies tracing experiments to characterize the patterns of inputs to different LS projection populations. Additionally, we performed cellular resolution calcium imaging in different positions along the DV axis of the LS during an operant reward task to determine how reward responses are organized along the DV axis of the LS. We did not find significant differences in proportions of input neurons to the projection populations in our tracing experiments suggesting that different LS projection populations receive similar patterns of inputs across various brain regions. We found interesting differences in the reward-related activity along the DV axis suggesting that dorsal and ventral populations of LS likely play different roles in reward-related behaviors. Future studies will be required to further ascertain the identities of the imaged neurons and the causal role they play in mediating behavior.

Disclosures: **S. Karkare:** None. **J. Isaac:** None. **M. Malavika:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NKFI (2020-2.1.1-ED-2021-00190)
NKFI (2020-2.1.1-ED-2022-00208)

Title: Cortex-wide mechanism of reinforcement signaling via a cholinergic pathway

Authors: *Z. SZADAI[1], Q. CHEVY[2], L. POPARA[1], A. KEPECS[2], B. RÓZSA[3,1];
[1]BrainVisionCenter, Budapest, Hungary; [2]Washington Univ. Sch. of Med., Washington Univ. in St. Louis, St. Louis, MO; [3]Inst. Exptl. Med., Budapest, Hungary

Abstract: Reward and punishment powerfully inform ongoing behaviors and drive learning throughout the brain, including the neocortex. Yet it remains elusive how these global signals reach the cortex, how they are represented there and how they impact local cortical computations. To address these questions, we used 3D random-access two-photon microscopy to monitor neural activity in dozens of cortical areas while mice performed simple auditory decision tasks. We found that VIP and SOM interneurons were recruited differently by reinforcers during the initial learning procedure. The rapid, cortex-wide activation of most VIP interneurons upon reinforcement was mirrored in the acetylcholine release recorded at the vicinity of the VIP cells, implying that this neuromodulator may be responsible for the transmission of reinforcement signals. We suggest that this acetylcholine-dependent global response mode of VIP cortical inhibitory neurons provides a cell-type-specific circuit mechanism by which organism-level information about reinforcers regulates local circuit processing and plasticity.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant DA045463
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Title: Dorsal hippocampus to nucleus accumbens projections drive reinforcement via activation of accumbens dynorphin neurons

Authors: *K. IBRAHIM[1], N. MASSALY[2], H.-J. YOON[1], R. SANDOVAL[1], A. WIDMAN[1], S. WILLIAMS[1], W. POST[1], S. PATHIRANAGE[1], T. LINTZ[1], A. ZEC[1], A. PARK[1], W. YU[3], T. KASH[3], R. W. GEREAU, IV[1], J. MORON-CONCEPCION[1];
[1]Anesthesiol., Washington Univ. in St. Louis, St. Louis, MO; [2]Anesthesiol., UCLA, Los Angeles, CA; [3]UNC- Chapel Hill, UNC- Chapel Hill, Chapel Hill, NC

Abstract: The hippocampus represents a key structure in the integration of emotional processing, learning and memory, and reward-related behaviors. While the ventral subdivision of the hippocampus (vHPC) is involved in processing emotional values of salient stimuli and goal-directed behaviors, the dorsal hippocampus (dHPC) plays a critical role in episodic, spatial, and associative memory. In addition, it has been shown that the dHPC is necessary for context- and cue-associated reward behaviors, including the expression of reward seeking. The nucleus accumbens (NAc), a central structure in the mesolimbic reward pathway, integrates the salience of aversive and rewarding stimuli and its activity is sufficient to drive aversive and appetitive behaviors. Recent evidence has demonstrated that dHPC->NAc pathway is necessary for the expression of a conditioned place preference. However, despite years of groundbreaking research and identification of direct projections from the dHPC to the NAc, the sufficiency for excitatory neurons in dHPC ($dHPC^{CaMKII)}$->NAc inputs to drive reinforcement and reward-associated behavior remains to be determined.
In this study, we used a wide range of complementary techniques including operant behavior, *in-vivo* manipulation using optogenetics, chemogenetics, and fiber photometry recordings to demonstrate that activation of $dHPC^{CaMKII}$->NAc pathway is sufficient to drive reinforcing behaviors via enhanced glutamatergic signaling in the NAcSh. Although stimulation of $dHPC^{CaMKII}$ neurons activates both enkephalin (Enk)- and dynorphin (Dyn)-containing medium spiny neurons (MSNs) in the NAcSh in male and female mice, only Dyn-containing MSNs mediates $dHPC^{CaMKII}$-induced reinforcing behavior. Our *ex-vivo* recordings in NAcSh slices determine the $dHPC^{CaMKII}$ neurons synapse directly to Dyn-containing neurons selectively in the dorsomedial part of the NAcSh, while they synapse into Enk-containing MSNs more broadly through the NAcSh. Our findings shed light on a novel pathway governing reinforcement and further extend the role of the dHPC on reward seeking.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Topic: G.02. Reward and Appetitive Learning and Memory

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Title: Charting the trajectory of impulsive and motivated behavior across adolescent development in mice

Authors: *R. ALBERT-LYONS, K. H. NG, K. M. NAUTIYAL;
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Abstract: Adolescence is a developmental phase that has been characterized by increased impulsive behavior, reward seeking, and maladaptive decision-making. The interdependence of these phenotypes and the trajectory of their maturation is not fully understood. Traditional behavioral and neural methods for studying adolescent development in rodents have limited our study to mostly static snapshots. Our approach for automated homecage behavioral testing allows for longitudinal assessment of complex phenotypes and their neural substrates throughout adolescent development in mice. Using our DIY-Nautiyal Arduino Modular Instrumental Conditioning (DIY-NAMIC) homecage behavioral system as well as additional commercial systems, we were able to test impulsive action, delay discounting, and reward and cue valuation on a time-scale consistent with the relatively short period of mouse adolescence. We measured these behaviors across the extent of mouse adolescent development ranging from post-weaning through adulthood to assess the trajectory of behavioral maturation of these different phenotypes to adult levels. We measured impulsive action using a two-choice serial reaction time task (2-CSRTT) as well as cue and reward-related behaviors through conditioned reinforcement, incentive salience, and hedonic drive. We found large increases in the hedonic response to rewards in adolescent mice, as early as postnatal day 34 (PN 34), compared to adults as measured by their increased preference for palatable rewards in a lickometer assay. Early adolescent mice also showed more incentive salience compared to adults displaying increased sign-tracking behavior, but no differences in learning or goal tracking behavior. Additionally, there was a small negative correlation between age and impulsive action from PN40 through adulthood, measured by premature responses in the 2-CSRTT. There were also no significant differences in conditioned reinforcement between adolescent and adult mice. Overall, we show that early adolescent mice have an exaggerated reward drive compared to adults, and more limited increases in impulsivity. Ongoing work is aimed at determining differences in the temporal patterns of the adolescent maturation of hedonic drive and impulsivity. Characterization of the trajectories and phenotypic interactions in adolescent mice is important for studies investigating the neural developmental changes that support behavioral maturation of impulsive and reward-related behavior.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Title: The role of serotonergic input to the paraventricular thalamus in reinforcement learning

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Abstract: Background: The paraventricular thalamus (PVT) serves as a hub that links hypothalamic and monoaminergic inputs to the amygdala, nucleus accumbens, and cortical areas for adaptive behaviors. PVT has been shown to receive strong serotonergic projections from the raphe nuclei. Since previous studies showed that serotonin neurons regulate the effects of prior choice-outcome experiences in future decision-making and PVT neurons predict values of outcomes, it is possible that the serotonergic input to PVT has an important role in decision-making from prior experiences. Here we investigate the roles of PVT and its serotonergic input in reinforcement learning by optogenetic manipulation. Method: We used a probabilistic reversal learning (PRL) task in which mice chose between the left and right nose-poke ports for a water reward. Reward probabilities changed in blocks; left good (left = 0.7/right = 0.1) and right good (0.1/0.7) blocks. Blocks were changed randomly within 1 - 10 trials after an exponential moving average (tau = 8 trials) of better choice reached 75%. We used wild-type mice with AAV-hsyn-Jaws injection (n=4) for optogenetic inhibition of PVT neurons, and Tph2-ChR2(C128S) transgenic mice (n=4) for terminal stimulation of serotonergic projections to PVT. Optogenetic illumination was applied from when mice poked the center nose-poking port for trial initialization until the end of a trial. Result: Neither optogenetic inhibition of PVT neurons nor activation of serotonergic projection to PVT alter the number of trials to achieve block change. We quantified the change of choice behavior by optogenetic manipulation using a logistic regression model of the probability of choice based on the rewarded and unrewarded choices in the last six trials. Optogenetic inhibition of PVT neurons significantly decreased regression coefficients for both rewarded and unrewarded choices in the last trials (18 manipulation sessions, 18 control sessions, 95% credible intervals comparison). Optogenetic activation of serotonergic projection to PVT significantly increased the regression coefficient for the rewarded choice in the last trial (23 manipulation sessions, 20 control sessions, 95% credible intervals comparison). Conclusion: The results suggest that PVT neurons support repetition of the previous choice, and serotonergic input to PVT enhances the effect of reward experiences for the next choice.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

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Program #/Poster #: PSTR289.16/MM14

Topic: G.02. Reward and Appetitive Learning and Memory

Support: R15 MH121859 (Roman PI)

Title: Serotonin modulates habituation to novelty while drosophila explore

Authors: *G. ROMAN[1], **M. DE LA FLOR**[2], B. DAUWALDER[3], G. GUNARATNE[4], S. GARCIA[3], M. WANG[3], D. LE[3];
[1]Univ. of Mississippi, University, MS; [2]Univ. of Texas Hlth. Sci. Center, San Antonio, San Antonio, TX; [3]Biol. and Biochem., [4]Physics, Univ. of Houston, Houston, TX

Abstract: *Drosophila melanogaster* detect, learn about and respond to novelty in their environment. When introduced to a novel open field (OF), flies display initial robust levels of locomotor exploratory activity which decays over time. We hypothesized that the decreases in locomotor activity signifies habituation, a form of non-associative learning, in response to the novelty presented by the OF. To test this hypothesis, we employed a dishabituation assay that allowed us to detect not only habituation but also dishabituation and habituation to dishabituation in the OF, all of which are key characteristics of habituation. However, understanding of the underlying mechanisms involved in modulating locomotor activity during habituation to novelty in the fly brain remains limited. Serotonin (5-HT) is a known neuromodulator of important behaviors like arousal, attention, sleep, aggression, and learning and memory. Thus we hypothesized that 5-HT may play a role in habituation to novelty in flies. Our results show that pharmacological manipulation 5-HT signaling with 5-HTP or α-MTP increased and decreased habituation to novelty respectively. Moreover, we show that optogenetic and thermogenetic activation of neurons targeted by Trh-Gal4 was sufficient to increase habituation to novelty. We also show that optogenetic and thermogenetic activation or inhibition of the 5-HT secreting Dorsal Paired Medial neurons (DPMn) increased habituation to novelty. Further, through genetic rescue experiments we show that the 5-HT1A receptor is required in the α/β and γ neurons of the mushroom bodies (MB) for habituation to novelty to occur. Together, our work suggests a putative DPMn-MB 5-HT circuit that may regulate exploratory locomotor activity in response to learning and contribute to a broader understanding how behaviors are regulated.

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Poster

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Topic: G.02. Reward and Appetitive Learning and Memory

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K08MH110610

Title: 5ht2c but not 5ht1b receptors in the nac constrain the rewarding effects of mdma

Authors: *S. VAILLANCOURT[1], M. POMRENZE[2], R. C. MALENKA[3], B. HEIFETS[1]; [1]Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Stanford, CA; [3]Dept Psychiat, Stanford Univ. Sch. Med., Palo Alto, CA

Abstract: Intro: 3,4-methylenedioxymethamphetamine (MDMA) is a substituted amphetamine with prosocial and rewarding effects. These properties may be driven by efflux of serotonin (5-HT) and dopamine (DA) via action at their respective transporters, SERT and DAT, in the Nucleus Accumbens (NAc). While MDMA is considered a drug of abuse, it has less addiction liability compared to other psychostimulants. Understanding the distinct 5HTergic and DAergic mechanisms underlying MDMA's effects may lead to valuable insights for development of prosocial therapeutics in treating PTSD and other psychiatric conditions.
Methods: Behavior: Conditioned Place Preference (CPP; reward learning); 3 Chamber Test (3CT; social exploration). Drugs: MDMA (5, 7.5, 15 mg/kg), Fenfluramine (FEN, 10 mg/kg), Methamphetamine (METH, 2 mg/kg) Mouse lines: C57BL/6 (wild-type; WT); tamoxifen-induced conditional DAT and SERT-KO. Drug Microinfusions: SERT, 5-HTR1b, and (S)-citalopram (SCIT, 0.5 µg), NAS-181 (0.5 µg) or SB242084 (1 µM) respectively. Fiber Photometry: DA release in NAc was measured by viral fluorescent reporter (AAV-hSyn-GRAB-DA-4).
Results: Low-dose MDMA (7.5 mg/kg) and FEN promote social exploration but not CPP, whereas METH promotes CPP but not social exploration. High dose MDMA (15 mg/kg), which promotes CPP, and METH promote similarly large increases in GRAB-DA fluorescence in NAc, compared to MDMA 7.5 mg/kg and FEN. Conditional deletion of DAT significantly reduced MDMA-dependent (15 mg/kg) reward learning and MDMA-evoked DA release. Conditional deletion of SERT abolished MDMA-dependent (7.5 mg/kg) social exploration but promoted CPP at a subthreshold dose of MDMA (5 mg/kg) with minimal behavioral effects in WT mice. Blocking SERT and 5-HTR2c, but not 5-HTR1b, in the NAc enhanced CPP with subthreshold MDMA. NAc microinfusion of either SCIT or SB242084 significantly enhanced DA release evoked by subthreshold MDMA.
Discussion: These data support a model of MDMA action wherein 5-HT mediates acute social exploration and DA mediates nonsocial drug reward, but not acute social exploration. Several manipulations, including SERT cKO, intra-NAc infusion of SCIT, or a 5-HTR2c antagonist all converted a low, non-rewarding dose of MDMA into one that supports CPP, and these manipulations all enhance DA release in NAc evoked by low dose of MDMA. Interestingly, the mechanism of MDMA-mediated prosocial behavior, requiring 5-HTR1b, differs from the mechanism whereby MDMA-evoked 5-HT release constrains nonsocial MDMA reward. Altogether, our results suggest that MDMA-induced 5-HT release modulates DA release and MDMA CPP through activation of 5-HT2c receptors in the NAc.

Disclosures: S. Vaillancourt: None. **M. Pomrenze:** None. **R.C. Malenka:** None. **B. Heifets:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.18/MM16

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant DA054370

Title: An investigation into the anatomical distribution and transcriptional heterogeneity of GABA neurons in the ventral tegmental area and rostromedial tegmental nucleus

Authors: *Z. J. HOUGH[1], B. HUGHES[2], C. COWAN[3], T. JHOU[1];
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Abstract: Increasing evidence indicates substantial heterogeneity in the function and gene expression of ventral midbrain GABAergic neurons, which play a critical role in the regulation of motivated behavior. Accordingly, further elucidation of the molecular differences between distinct populations of GABA neurons and their topographical distribution is needed. In this study we focused primarily on two distinct regions of the midbrain known to regulate motivated behavior, the ventral tegmental area (VTA) and the rostromedial tegmental nucleus (RMTg, also known as the tail of the VTA). Importantly, nearly one third of the VTA is comprised of GABA neurons, which are increasingly recognized as heterogeneous. Interestingly, in situ hybridization (ISH) revealed a dense cluster of neurons that co-express *th*, *vgat* and *gad2*, but not *gad1*. Notably, *th* levels in this subpopulation was markedly lower than in *th* cells lacking *vgat* or *gad2*. In contrast to the VTA, RMTg neurons are almost entirely GABAergic, but less is known regarding their potential heterogeneity or whether they overlap with any subpopulations of VTA GABA neurons. Accordingly, we performed single nuclei RNA sequencing of VTA and RMTg tissue from four approximately 12-week-old male Sprague Dawley rat brains. Tissue from each region was isolated and processed independently to allow comparison of gene expression between cells of both brain regions. Preliminary analysis of these data sets corroborates previous findings of ourselves and others regarding heterogeneity of VTA GABA neurons, including the existence of a distinct subset containing *th* transcripts. Additionally, we confirmed that *foxp1* expression, found in over 90% of RMTg GABA neurons, distinguishes RMTg from VTA GABA neurons, consistent with prior immunohistochemical (IHC) and ISH findings. Ongoing analysis of these datasets, along with topographical characterization using IHC and ISH, will further elucidate distinct subtypes in these brain regions. In conclusion, RMTg GABA neurons are transcriptionally distinguishable from VTA GABA neurons, suggesting differing roles in the regulation of motivated behavior. Additionally, our findings further corroborate the heterogeneous nature of VTA GABA neurons and indicate the need for further investigation into their functional roles.

Disclosures: **Z.J. Hough:** None. **B. Hughes:** None. **C. Cowan:** None. **T. Jhou:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.19/MM17

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NHMRC Ideas Grant APP2011633
Australian Government Research Training Program (RTP) Scholarship

Title: Diversity and topology of inputs to the paraventricular thalamus associated with motivated behaviour

Authors: *S. R. GILCHRIST[1], E. CHOI[2], G. P. MCNALLY[2], J. M. POWER[3];
[2]Sch. of Psychology, [3]Translational Neurosci. Facility & Dept. of Physiol., [1]Univ. of New South Wales, Sydney, Australia

Abstract: Appetitive and aversive motivation are critical in our interaction with the environment. However, the neural circuitry underlying competition between these opposing motivations is not well understood. Recent studies have established a functional role of the paraventricular thalamus (PVT) in this competition. This has been linked in part, to inputs from multiple brain regions, including the periaqueductal gray (PAG) and the hypothalamus providing the PVT with interceptive and exteroceptive sensory information; inputs from the medial prefrontal cortex (PFC) providing possible control over these processes; and PVT projections to the nucleus accumbens shell. However, the nature of these projections to the PVT and their interactions with each other remain poorly characterised. We used whole-cell patch-clamp electrophysiology and optogenetic techniques in male and female Long Evans rat brain slices to map the characteristics and topographical organisation of PVT inputs. Retrograde tracer in the nucleus accumbens shell allowed for targeted recordings of PVT output neurons to build up a larger understanding of the circuitry. The GAD1 subpopulation of the hypothalamic input was also investigated with a combination of electrophysiology and RNAscope techniques to further understand this component. We found that inputs from the PFC were excitatory and topographically biased. Light evoked EPSCs were observed in 39 of 44 (89%) neurons in the posterior PVT and only in 4 of 12 (33%) neurons in the anterior PVT. Meanwhile, ascending inputs from the PAG and hypothalamus were mixed and showed no anterior-posterior topography. Light-evoked inhibitory currents from these inputs were recorded in 24% of 111, and 58% of 85 PVT neurons, while EPSCs were observed in 13% and 32% respectively. Crucially, this mixed excitatory/inhibitory input was preserved even when isolating PVT inputs from hypothalamic GAD1 neurons, though with a higher predominance of EPSCs (27 of 63; 43%) than IPSCs (16 of 63; 25%). RNAscope revealed a small population of GABA and Glutamate co-expressing neurons (0.7%) in the hypothalamus that may account for some of this mixed profile. The high rates of connectivity suggest convergence of diverse input pathways onto individual PVT neurons and possible integration prior to relay to ventral striatal regions for behavioural control. Moreover, heterogeneity in ascending pathways, and their convergence with

the descending PFC input suggests complexity in how these circuits drive behaviour and how they may be dysregulated following exposure to stressors or drugs of abuse.

Disclosures: S.R. Gilchrist: None. **E. Choi:** None. **G.P. McNally:** None. **J.M. Power:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.20/MM18

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NHMRC Ideas Grant GNT2011633
University of New South Wales University International Postgraduate Award Scholarship

Title: Ventral striatopallidal pathways to lateral hypothalamus in alcohol-seeking

Authors: *S. LUI[1], J. M. POWER[2], G. P. MCNALLY[3];
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Abstract: The ventral striatopallidal system, consisting of nucleus accumbens and ventral pallidum (VP), is a key component of the reward system and plays a role in alcohol use disorder. We have previously shown that inhibitory projections from the nucleus accumbens shell (AcbSh) and the VP to the lateral hypothalamus (LH) have opposing actions: preventing and promoting relapse to alcohol-seeking respectively. The AcbSh also projects to the VP directly; however, the circuitry relationship between this connection and the VP to LH connection is poorly understood. To address this, we used channelrhodopsin (ChR2)-assisted circuit mapping and retrograde tracing techniques. Specifically, we used transgenic D1-Cre and A2A-Cre Long Evans rats (n = 9) with Cre-dependent ChR2 to target AcbSh neurons and retrograde labelled LH-projecting VP neurons with mCherry. Whole-cell patch-clamp recordings of VP neurons revealed light-evoked postsynaptic responses that were inhibitory and picrotoxin-sensitive in a subset of neurons. We showed that putative non-LH-projecting VP neurons received input from D1- and D2-AcbSh cells (36% and 24% respectively), whereas LH projectors predominantly received D1-AcbSh input with minimal D2-AcbSh connections (38% and 4% respectively). So, whereas D1-AcbSh neurons provide input to both LH-projecting and non-LH projecting VP neurons, D2-AcbSh neurons preferentially synapse with non-LH projectors. These results show an indirect disynaptic pathway connecting D1-AcbSh neurons to LH via VP neurons. Past work has shown a direct projection from AcbSh to LH. This bifurcation in ventral striatopallidal pathways may bidirectionally regulate alcohol-seeking behaviour and ongoing studies are assessing plasticity in these pathways.

Disclosures: S. Lui: None. **J.M. Power:** None. **G.P. McNally:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.21/MM19

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH R01DA035443
NIH R01DA057084
NIH R21DA059233

Title: Central amygdala neurons are necessary for habit formation

Authors: *A. K. CRAWLEY[1], J. GIOVANNIELLO[2], M. MALVAEZ[3], K. M. WASSUM[4]; [1]UCLA Chapter, Los Angeles, CA; [2]Univ. of California Los Angeles, [4]UCLA, [3]UCLA, Los Angeles, CA

Abstract: When making decisions, we often consider possible future outcomes to help us make the best choice given our current circumstances. To do this, we rely on an internal model of our actions and their consequences. Such encoded **action-outcome (A-O) memories** support **goal-directed behavior**. Goal-directed decision making is, however, cognitively taxing. So, humans and other animals have another strategy for more routine behaviors: **habits**. Habits are formed with repeated practice and allow routine behaviors to be executed more automatically based on their past success, rather than forethought of their consequences. We balance goal-directed decisions and habits to allow behavior to be adaptive when needed, but efficient when appropriate. Disruptions to this balance can contribute to addiction and mental illness. There is much unknown about the neural circuitry that supports action-outcome goal-directed learning and habit formation. The central amygdala (CeA) is one brain region that has been implicated in habit. The goal of this project is to reveal how the CeA regulates habit formation. We hypothesized that CeA activity is necessary at the time of reward experience to form habits. To test this, we optogenetically inhibited CeA neurons at the time of reward delivery during each day of training on an instrumental lever press-food reward task in male and female rats. Rats were overtrained on a random interval schedule of reinforcement to promote habit formation. Whereas controls formed habits, as evidenced by insensitivity to post-training outcome-specific devaluation or omission contingency, inhibition of the CeA prevented habit formation, resulting in continued sensitivity to outcome-specific devaluation or omission contingency. Thus, the CeA is necessary for habit formation. Ongoing work is assessing how dopaminergic inputs into the CeA contribute to habit formation.

Disclosures: A.K. Crawley: None. **J. Giovanniello:** None. **M. Malvaez:** None. **K.M. Wassum:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.22/MM20

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH R01DA046679
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NIH F32DA056201
A.P. Giannini Fellowship
NIH TL4GM118977

Title: Opposing amygdala-striatal pathways enable chronic stress to promote habit formation

Authors: *J. GIOVANNIELLO[1], N. PAREDES[6], A. WEINER[2], C. ORAGWAM[3], H. UWADIA[2], G. NNAMDI[2], M. SEHGAL[7], F. M. REIS[2], A. SIAS[3], M. MALVAEZ[4], A. ADHIKARI[4], A. SILVA[5], K. M. WASSUM[4];
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Abstract: When making decisions, we prospectively evaluate our potential actions and their predicted outcomes to choose an appropriate behavior. This goal-directed strategy allows us to adapt when situations change but it is cognitively taxing. Habits are a more efficient but less flexible strategy whereby behaviors are executed without forethought of their consequences, based on past success. Balance between these strategies allows behavior to be adaptive when needed, but efficient when appropriate. Overreliance on habit is characteristic of many psychiatric conditions, including addictions. Stress is a major contributing factor to these conditions. It also promotes habits. Thus, we sought to uncover the neuronal circuits that permit stress to promote habits. We established a model of stress-potentiated habit formation in mice using chronic mild unpredictable stress and subsequent reward-seeking instrumental conditioning. Mice with a history of chronic stress formed habits prematurely, as evidenced by insensitivity to outcome devaluation or omission contingency. The dorsomedial striatum (DMS) mediates goal-directed behavior and the amygdala is a stress hub. Therefore, we next used a multifaceted approach to expose the contribution of amygdala-striatal projections to goal-directed learning and stress-potentiated habit formation. The basolateral amygdala (BLA) sends a direct excitatory projection to the DMS. We found that these neurons are activated during instrumental learning and that this activity is critical for the action-outcome learning that supports goal-directed behavioral control. Stress dampens this to disrupt action-outcome learning and promote habit formation. Activating this pathway during post-stress learning restores normal goal-directed behavioral control. A direct central amygdala (CeA) projection to the dorsal striatum was recently identified. We found that CeA neurons target DMS and inhibit striatal projection neurons. CeA-DMS projections are not typically robustly activated during goal-directed learning, but stress recruits activity in this pathway to promote habit formation. Inhibition of the CeA-DMS pathway during post-stress learning prevents habit formation. This establishes the first functional role for the CeA-DMS pathway in modulating behavior. Together,

these data reveal that stress disrupts the balance between two opposing amygdala-striatal projections to prevent the learning that underlies adaptive decision making and promote the formation of premature inflexible habits. NIH R01DA046679 (KW), NIH T32DA024635 (JG), NIH F32DA056201 (JG), A.P. Giannini Fellowship (JG), and NIH TL4GM118977 (NP).

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.23/MM21

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant DA035443

Title: Cell-type specific contributions of striatal projection neurons to goal-directed and habit learning

Authors: *M. MALVAEZ, A. LIANG, J. GIOVANNIELLO, A. WIKENHEISER, K. WASSUM;
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Abstract: Optimal behavior relies on a balance between two distinct strategies. During goal-directed decision making the relationship between actions and their consequences is considered to enable adaptive choices. Habits allow routine tasks to be conducted more automatically, without forethought of their consequences. The balance between these systems allows behavior to be adaptive when needed and efficient behavior when appropriate. But disruption of this balance can lead to symptoms characteristic of several psychiatric and neurological diseases. Goal-directed behavior relies on the dorsomedial striatum (DMS). Little is known about the contribution of the two major striatal projection neurons (SPNs) subtypes: direct (characterized by D1 receptor expression) and indirect (characterized by A2A receptor expression) pathway projections. Using cell-type specific cellular resolution microendoscopic calcium imaging and chemogenetic manipulation coupled with instrumental lever press - food reward conditioning and outcome-specific devaluation tests, we characterized the function of these two DMS neuron subtypes in goal-directed learning. DMS D1 neurons are active throughout instrumental learning, especially around action initiation. The dSPN ensemble that represents action initiation is stable from early goal-directed learning through the transition to habit. Correspondingly, DMS D1 neurons are required for goal-directed learning and the expression of goal-directed behavior. DMS D1 neuron activity is also sufficient to promote goal-directed behavioral control even after overtraining, which would normally enable habit. DMS A2A neurons are also active during instrumental learning around action initiation. However, the A2A ensemble representing action

initiation shifts as behavioral control transitions from goal-directed to habitual. Accordingly, DMS A2A neurons are necessary for early goal-directed learning, but are insufficient to promote goal-directed behavior after overtraining. Thus, DMS D1 and A2A neurons have coordinated function to promote the action-outcome learning that supports flexible goal-directed behavioral control early in learning. But only D1 neurons maintain a representation of goal-directed actions as habits form, whereas A2A neurons lose such a representation and instead come to represent habitual behavior.

Disclosures: M. Malvaez: None. **A. Liang:** None. **J. Giovanniello:** None. **A. Wikenheiser:** None. **K. Wassum:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.24/MM22

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA Grant R01DA053208

Title: Ventral pallidal GABAergic neurons drive consumption in a sex-dependent manner

Authors: *A. PAULSON, A. SCOTT, C. PRILL, B. NEWELL, J. RICHARD;
Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Food intake is controlled by multiple converging signals: hormonal signals that provide information about energy homeostasis, but also hedonic and motivational aspects of food and food cues that can drive non-homeostatic or “hedonic” feeding. The ventral pallidum (VP) is a brain region implicated in the hedonic and motivational impact of food and foods cues, as well as consumption of rewards. Disinhibition of VP neurons has been shown to generate intense hyperphagia, or overconsumption. While VP gamma-Aminobutyric acidergic (GABA) neurons have been implicated in cue-elicited reward seeking and motivation, the role of these neurons in the hyperphagia resulting from VP activation remains unclear. Here, we used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to activate or inhibit VP GABA neurons in sated male and female rats during chow and sucrose consumption. Long Evans rats (n = 62, 32 males [M], 30 females [F]) received bilateral infusions of a GAD1-cre virus mixed with a cre-dependent virus for either Gq DREADD (n=23, 12M, 11F), Gi DREADD (n=25, 13M, 12F), or mCherry control (n=14, 7M, 7F). Rats were habituated for three days to 1-hour access to sucrose or chow, and then tested with injections of a DREADD ligand, JHU37160 dihydrochloride (JHU; 0.05 and 0.5 mg/kg), and saline, on separate test days, counterbalanced for order. Following behavioral testing, a subset of rats was perfused following a ligand or saline injection and immunohistochemistry was performed to examine c-fos and DREADD colocalization. We found that activation of VP GABA neurons increases consumption of chow and sucrose in male rats, but not female rats. We also found that, while inhibition of VP GABA neurons tended to

decrease sucrose consumption, this effect was not significant. As expected, injections of DREADD ligand increased the proportion of DREADD-expressing cells that were cfos-positive. Together, these findings suggest that activation of VP GABA neurons can stimulate consumption of routine or highly palatable rewards selectively in male rats.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.25/MM23

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA Grant R01DA053208

Title: Ventral pallidal encoding of expected outcome value evoked by Pavlovian cues

Authors: *A. SOOD[1], T. TRAN[2], M. CRISTOFORO[2], A. WALSH[2], J. M. RICHARD[2]; [1]Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Neurosci., Univ. of Minnesota, Twin cities, Minneapolis, MN

Abstract: Goal-directed behavior relies on accurate mental representations of outcomes and their expected value to guide decision making. Disruptions to this process are a core component of several neuropsychiatric conditions, including addiction. Understanding the neural mechanisms underlying expected value encoding is therefore key to developing effective long-term treatments for addiction. The Ventral Pallidum (VP) is a basal forebrain region that is important for motivation and reward processing. Cue-evoked activity in populations of VP neurons is known to encode the expected value of rewards. Yet, the impact of outcome (reward) devaluation on these neural responses to cues has not been assessed. Outcome devaluation involves reducing the value of the expected outcome and is a classic test of goal-directed behavior that can be used to test whether these neural responses to cues reflect the expected value or merely other factors that correlate with the expected value. In this study, we used *in-vivo* electrophysiology to record from single units in the VP of male and female Long Evans rats responding to Pavlovian reward cues before and after reward devaluation. Adult rats were trained with an auditory conditioned stimulus (CS+) that signaled the delivery of a 10% sucrose reward and a control cue (CS-) that never predicted a reward. They then underwent reward devaluation via sensory-specific satiety where they were allowed free access to either 10% sucrose or a control substance (maltodextrin) immediately followed by testing under extinction conditions. We recorded from the VP of these rats during training, free access, and testing under extinction. We found that many VP neurons were excited by the CS+ and that these neurons were more responsive to the CS+ than the CS-. Additionally, VP responses to the CS+ were reduced after free consumption of sucrose. Interestingly, free access to maltodextrin also reduced VP

responses to the CS+, suggesting that these changes in VP responding were probably not due to the encoding of the sucrose reward specifically. Behaviorally, both male and female rats displayed a reduced probability to enter the reward port during the CS+ after free access to sucrose, but only male rats showed a reduction in the latency to enter the port during the CS+ following devaluation. Future experiments will test whether cue-evoked excitations in VP neurons specifically reflect the expected outcome value or a general change in motivation due to the consumption of a sweet-tasting substance and whether encoding of the expected outcome value is sex-dependent.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.26/MM24

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Alcohol-paired cues drive aversion-resistant drinking in Long Evans rats

Authors: *M. LORTIE, L. BUSHAGOUR, T. TRAN, R. HARIHARAN, E. GALLIGHER, J. RICHARD;
Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Alcohol-paired cues drive aversion-resistant drinking in Long Evans rats
Authors
***M. LORTIE**, L. BUSHAGOUR, T. TRAN, R. HARIHARAN, E. GALLIGHER, J. RICHARD;Neurosci., Univ. of Minnesota, Twin Cities, Minneapolis, MN
Disclosures
M. Lortie: None. **L. Bushagour:** None. **T. Tran:** None. **R. Hariharan**: None. **E. Galligher:** None. **J. Richard:** None.
Abstract
Alcohol use disorder is often characterized by compulsive alcohol use in the face of negative consequences. One model of compulsive-like alcohol seeking and consumption is aversion-resistant drinking, in which animals continue to drink alcohol despite its adulteration with quinine, a bitter substance. Cues associated with alcohol and other drugs have also been shown to increase craving, self-administration, and relapse-like behavior, but the effect of cues on aversion-resistant drinking has not yet been examined. Here, we assessed the influence of alcohol-paired cues on aversion sensitivity during alcohol self-administration in Long Evans rats (n=24; 12 males and 12 females). Following 4-6 weeks of intermittent access to 15% EtOH in their home cages, rats were trained to self-administer 15% EtOH in operant boxes for up to 17 sessions. During 1 hour self-administration sessions, presses on the active lever resulted in a delivery of 0.1 mL 15% EtOH to the reward port, and presentation of the alcohol cue, which

consisted of a white noise and stimulus light simultaneously presented for 5 seconds. Presses on the inactive lever had no programmed consequences. Following stabilization of responding, rats were tested under the following conditions for at least 4 days each: 1) 15% EtOH with cues, 2) 15% EtOH + 45 mg/L quinine with cues, 3) 15% EtOH without cues, and 4) 15% EtOH + 45 mg/L quinine without cues. When rats were tested with cues, we found that quinine failed to suppress both operant responding and consumption of alcohol. If anything, alcohol self-administration increased under the presence of cues. In contrast, when cues were removed, quinine reduced self-administration, as well as consumption. We saw a similar effect of cues on quinine sensitivity in male and female rats, though they differed in overall responding, with males completing more active lever presses as baseline. Overall, our data suggest that alcohol-paired cues can modulate sensitivity to aversive stimuli during alcohol seeking and consumption, potentially leading to compulsive-like alcohol seeking. Future work is needed to better understand the influence of cue-elicited appetitive motivation on behavioral and neural mechanisms governing the suppression of behavior by aversive stimuli.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.27/MM25

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA Grant R01DA053208

Title: Ventral pallidal GABA neurons are necessary for the invigoration of reward-seeking by cues

Authors: *B. A. NEWELL[1], I. D. LIN[2], D. PALMER[3], A. SCOTT[4], A. PAULSON[1], P. MURUGANANDAN[3], P. REMDE[3], J. M. RICHARD[4];
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Abstract: The ventral pallidum (VP) is an important target structure for the investigation of addiction and relapse due in part to its role in cue-elicited reward-seeking behavior. Prior research has demonstrated that VP GABA neurons are excited by reward cues and are necessary for context renewal of alcohol-seeking. Yet, their role in the invigoration of reward-seeking by discrete cues remains unclear. Here, we used optogenetics to assess the impact of phasic cue-paired manipulations of VP GABAergic neurons on reward-seeking behavior in a discriminative stimulus task (DS task). To target VP GABA neurons, male and female Long Evans rats received bilateral VP injections of a GAD1-Cre recombinase viral vector combined with a viral vector for cre-dependent expression of either inhibitory opsin, excitatory opsin, or non-opsin control

protein. After the rats recovered, they were trained in the DS task, in which presentations of an auditory DS cue indicated availability of 10% sucrose reward. Port entries during the DS (auditory) cue resulted in sucrose delivery, while port entries during a neutral stimulus (NS) auditory cue did not. Once rats learned to discriminate between the cues, they performed optogenetic test sessions in which 50% of DS and NS presentations were paired with either 1s or 10s of laser inhibition, excitation, or control manipulations. Inhibition for the duration of the DS (up to 10s) reduced response likelihood and increased response latency. In contrast, during sessions with brief 1s inhibition, port entry likelihood was reduced during the 1s inhibition, but rebounded afterwards. Similarly, port entry likelihood rebounded after inhibition offset during the NS, perhaps due to rebound excitation. Exciting VP GABA neurons did not significantly impact reward seeking on DS trials, but laser-paired NS excitation trials yielded higher response ratios and quicker responding for both 1s and 10s sessions. Altogether, our findings suggest that VP GABA neurons contribute to response invigoration by reward cues. Future experiments will examine the contributions of VP GABA neurons to the ability of reward cues to invigorate separately trained or novel reward-seeking behaviors.

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Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.28/NN1

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH BRAIN R00 DA048749
One Mind Foundation
Brain Research Foundation

Title: Elucidating the INS^{Nos1}-$CeA^{Pkc\ \delta/SST}$ circuit during non-homeostatic feeding behaviors

Authors: *A. L. RIVERA, S. STERN, M. OLVERA-CALTZONTZIN, Y.-S. HWANG;
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Abstract: Feeding is pivotal for all living beings to survive, by maintaining bodily homeostasis. However, these behaviors can be disrupted and become maladaptive, resulting in various pathologies such as obesity and diabetes. Gaining a comprehensive understanding of how the brain regulates feeding behaviors and the impact of disruptions in this process is vital for our pursuit of potential treatments. The Insular Cortex (INS) is hypothesized to be important for the processing and regulation of internal signals and has a role in feeding behaviors. Previous results from the lab showed that nitric oxide synthase 1 (Nos1) neurons in the INS have an important role on appetitive non-homeostatic feeding behaviors, particularly overconsumption. Additionally, these neurons project to the central amygdala (CeA). By using retrograde tracing in

combination with fluorescent in situ hybridization, we found that INS^{Nos1} directly project to CeA, and particularly to two subpopulations, Protein Kinase C delta (PKC-δ), which are anorexigenic, and somatostatin interneurons (Stern et al., 2021). To gain a better understanding of this circuit we used a intersectional genetic and calcium recording approach to elucidate the functional connectivity between these two areas during feeding behavior. Using three transgenic mouse lines (Nos1-Cre/PKC δ -Flp or Nos1-Cre/SST-Flp), we injected a Cre-dependent Gq DREADD virus to target INS^{Nos1} neurons for activation and a Flp-dependent GCaMP6s virus with an optic fiber to simultaneously record neural activity of Pkc δ or Sst CeA neurons during a feeding behavior task. To first understand how this circuit works during eating, we fast mice and did calcium recordings during food presentation, then, we activate the INS^{Nos1} neurons, and record the calcium activity, once these two pathways where, separately, activated. We first observed, that the activation of INS^{Nos1} neurons increases food intake, in line with our previous observations that inhibition of these neurons prevents overconsumption. Additionally, activation of INS^{Nos1} may change calcium activity in the $CeA^{Pkc\ \delta/SST}$ neuronal populations before and after food approach. This suggests that the INS^{Nos1}-$CeA^{Pkc\ \delta/SST}$ circuit is important for appetitive feeding behaviors. Further experiments will determine the dynamic of both $CeA^{Pkc\ \delta}$ and CeA^{SST} and their possible connectivity. These experiments will provide valuable insights into the complex neural mechanisms underlying non-homeostatic appetitive behaviors.

Disclosures: A.L. Rivera: None. **S. Stern:** None. **M. Olvera-Caltzontzin:** None. **Y. Hwang:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.29/NN2

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH R00
One Mind Foundation
Brain Research Foundation

Title: Deciphering Insula Ctx Circuits Governing Appetitive and Aversive Non-Homeostatic Feeding BehaviorsBehaviors

Authors: *M. OLVERA CALTZONTZIN[1,2], A. RIVERA[1], Y.-S. HWANG[1], K. HODUM[1], E. MIZRACHI[1], A. KANAKAM[1], S. A. STERN[1];
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Abstract: Although homeostatic feeding is vital for survival, nevertheless internal states or past experiences can disrupt this balance, leading to non-homeostatic feeding behaviors. Earlier studies have shown that the insular cortex (INS) has specific neural populations coding for appetitive and aversive stimuli. Yet, the mechanisms by which the INS regulates appetitive or

aversive feeding behaviors through different circuits remain unclear. Earlier work from the lab has shown that a glutamatergic population expressing nitric oxide synthase-1 (INS^{Nos1}) in the insular cortex is critical for non-homeostatic food overconsumption. Using chemogenetics, I confirmed that silencing INS^{Nos1} neurons decreases overconsumption, but, unexpectedly, the same manipulation enhances taste aversion. Notably, this inhibition did not affect anxiety-related tasks, memory formation, or homeostatic feeding, suggesting that there is no general impairment of function. To gain further insights into how INS^{Nos1} neurons regulate feeding behavior, we performed calcium recording using fiber photometry. Our results corroborated earlier findings, indicating that Nos1 neurons are responsive during overconsumption and play a significant role in aversive taste learning. Furthermore, our data suggest that these neurons may contribute to the detection of stimulus salience based on internal states (e.g., fed vs. fasted) and odor. To elucidate the upstream and downstream neural circuitry involved, we employed a combination of monosynaptic rabies tracing and in situ hybridization/immunohistochemistry. Our previous results suggest that INS^{Nos1} neurons project to both CeA-somatostatin and PKCd (protein kinase c-delta) neurons for appetitive behaviors such as overconsumption (Stern et al., 2021). Our new data suggest that INS^{Nos1} neurons receive inputs from the BLA and the hypothalamus, regions known to be involved in regulating aversive and internal state information, respectively. These findings indicate that the role of INS^{Nos1} neurons is primarily to regulate non-homeostatic feeding behaviors, perhaps based on the salience of food in the environment, particularly in non-homecage contexts. However, there is still a need for further experiments to fully understand the INS^{Nos1}-CeA and BLA-INS projections during non-homeostatic learning. In future studies, we aim to elucidate the precise mechanisms and functional implications of these projections. This knowledge will contribute to a deeper understanding of how the insula modulates appetitive and aversive responses, ultimately advancing our understanding of the neural basis of feeding behavior regulation.

Disclosures: **M. Olvera Caltzontzin:** None. **A. Rivera:** None. **Y. Hwang:** None. **K. Hodum:** None. **E. Mizrachi:** None. **A. Kanakam:** None. **S.A. Stern:** None.

Poster

PSTR289. Reward and Appetitive Learning: Circuit Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR289.30/NN3

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Brain Research Foundation
One Mind Foundation
NIH R00 DA048749

Title: Mechanistic evidences of corticosterone-induced food overconsumption

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Abstract: Eating disorders (ED) are very complex pathologies displaying strong comorbidities with a large variety of psychiatric disorders. Among them, major depression, anxiety and post-traumatic stress, are all largely associated with dysregulation of the hypothalamic pituitary adrenal axis. Indeed, this axis, also known as the stress axis, is over-stimulated leading to abnormal cortisol system activity. Yet, little is known about how stress, and more specifically cortisol, might contribute to feeding behavior alterations and possibly lead to eating disorders. Moreover, epidemiological studies reported higher prevalence of these disorders among women, suggesting sex differences regarding the physiopathology of ED. To that end, using subcutaneous releasing pellet as a chronic corticosterone administration (primary adrenal corticosteroid in rodents), we describe a food-overconsumption phenotype in both male and female mice accompanied with an increase in body weight. In order to better understand the different impact of corticosterone on the metabolic profile depending on sex, we studied both male and female metabolism in response to chronic corticosterone administration using metabolic chambers. Secondly, we aimed to identify which brain regions could be involved in corticosterone-induced overconsumption. The insular cortex (IC) is commonly known as a hub integrating multiple internal and external stimuli, and it has been shown to be involved in non-homeostatic feeding. As there is also growing evidence that IC is also involved in anxiety behaviors, we first focused our investigation on this structure. Using single cell sequencing, we identified mineralocorticoid and glucocorticoid receptor expressions within multiple IC cell types, supporting a direct effect of corticosterone on this structure. To probe the effect of corticosterone on the IC neuronal activity, we performed freely moving calcium imaging using IC synapsin-driven GCaMP7c expression and a prismatic lens allowing 90°-angled imaging from a median perspective, avoiding cumbersome cranial window procedure. Our preliminary data suggests a change in the global activity of IC neurons giving rise to a potential mechanistic pathway of corticosterone on feeding behaviors.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

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Program #/Poster #: PSTR290.01/NN4

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Ministerio de Ciencia e Innovación, PID2021-126477NB-I00
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ICREA, ICREA Academia 2018

Title: Activity in auditory and reward-related structures shows an inverted U-shaped response to melodies that vary in complexity and rated pleasure

Authors: *G. FÀBREGA-CAMPS[1], A. ARA[2], M. DEOSDAD DIEZ[1], S. NICOLAOU[1], V. B. PENHUNE[3], J. MARCO-PALLARÉS[1];
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Abstract: Musical pleasure depends on how well music meets or violates our expectations. Musical complexity, or how predictable or unpredictable a melody is, influences our preference and enjoyment. We tend to like melodies that are neither too simple nor too complex, but that balance familiarity and novelty. Previous studies have delineated the brain network involved in music pleasure, but the neural mechanisms behind the interaction between music reward and complexity is not yet well understood. In the current study, twenty-nine people participated in an fMRI study where they listened to musical excerpts of different degrees of predictability and rated how much they liked them. The melodies were artificially generated from the transitional probabilities of a natural Western grammar, and categorised into three levels of predictability according to the note-by-note information content. The use of grammar that mimics the conditional probabilities of musical notes to generate melodies allowed us to investigate in a controlled way how probabilistic expectations and subjective pleasure were related. Behavioural results replicated previous findings of an inverted U-shape relationship between predictability and liking. A consistent pattern of activation was also identified when performing a region of interest analysis (ROI) in areas of the reward network (including Nucleus Accumbens and ventromedial prefrontal cortex) and auditory cortex. These regions exhibited enhanced activity for intermediate predictability excerpts compared to both high and low complexity stimuli. These results suggest that the interaction between complexity of musical stimuli and musical pleasure arises from the activation of reward and auditory perception networks in the brain.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.02/NN5

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NINDS R37NS21135
CONTE Center PO MH109429
Brain Initiative U19NS107609-03
U01NS108916
NSF GRFP
Independent Research Fund, Denmark

Title: Asymmetric coding of reward prediction errors in human insula and dorsomedial prefrontal cortex

Authors: C. HOY[1,2], ***D. R. QUIROGA-MARTINEZ**[2,3], E. SANDOVAL[2], D. KING-STEPHENS[4,6], K. D. LAXER[5], P. WEBER[5], J. J. LIN[7], R. T. KNIGHT[2,8];
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Abstract: The signed value and unsigned salience of reward prediction errors (RPEs) are critical to understanding reinforcement learning (RL) and cognitive control. Dorsomedial prefrontal cortex (dMPFC) and insula (INS) are key regions for integrating reward and surprise information, but conflicting evidence for both signed and unsigned activity has led to competing proposals for the nature of RPE representations in these brain areas. Recently developed RL models allow neurons to be differentially sensitive to positive and negative RPEs, a property with the potential to explain coding diversity in human INS and dMPFC. Here, we use intracranially recorded high frequency activity (HFA) to show that this asymmetric coding strategy captures RPE coding diversity in these regions. We found neural populations responding to valence-specific positive and negative RPEs, as well as unsigned RPE salience, which are spatially interleaved within each region. Furthermore, directional connectivity estimates suggest a leading role of INS in communicating positive and unsigned RPEs to dMPFC. These findings support asymmetric coding across distinct but intermingled neural populations as a core principle in RPE processing and reconcile long-standing theoretical debates on the role of dMPFC and INS in RL and cognitive control.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.03/NN6

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant 5R01MH076136

Title: Assessing the Impact of Social Decision-Making and Stimulus Expectancy on Pain Sensation

Authors: *A. DEHGHANI[1], C. BANGO[2], S. E. PRABHU[3], T. WAGER[4];
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Abstract: How do people assess the negative utility of pain when choosing for themselves and others? And is the experience of pain altered by the social context of receiving it as a result of others' choices? We addressed both questions in a social decision-making study in which participants first made choices to accept a monetary payoff to cause pain to themselves or another person, and then experienced the outcome of other players' choices. Past studies have found that people are (a) hyper-altruistic, choosing more pain for themselves than others for a given payoff (Crockett et al., 2014), and (b) exhibit pain value curves with a characteristic nonlinearity, such that more extreme pain has increasing disutility (Coll et al., 2022). Effects of the choice context on pain experience are less clear. We hypothesized that pain may be experienced as more intense when another player chose a more intense stimulus (a stimulus expectancy effect) and when the monetary payoff for the other was higher (an unfairness effect). After an adaptive calibration to measure pain threshold and tolerance, participants (N=59) made a series of choices accept or reject heat pain paired with a monetary reward for themselves or for future participants (64 trials each, crossing 8 levels of pain based on their calibrated tolerance with 8 levels of monetary reward from $1-$8). To maintain incentive compatibility, participants received, at random, one of the choices. Then, they were told they would be receiving a random sample of decisions from previous participants' choices. In fact, choice cues and stimuli were experimentally randomized. Participants received a series of choice cues (intensity and monetary value, 48 trials) followed by painful thermal stimuli (high or low pain, randomly allocated). When making choices, participants accepted higher reward values for themselves vs. others ($t(177)= 2.364$, $p = 0.019$) but there was no effect by pain on decisions for self vs. others. When experiencing others' choices, higher intensity cues and higher monetary payoff for another player caused increases in perceived pain for a given stimulus (p-tolerance_cue = 2.434e-06, Cohen's d-tolerance_cue = 0.734, p-monetary = 0.00791, Cohen's d-monetary = 0.224). Overall, the study revealed a difference in participants' decisions to accept pain paired with monetary values for themself vs others. The findings demonstrate novel effects in stimulus expectancy and social cognition on pain experience.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

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Program #/Poster #: PSTR290.04/NN7

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NSF BCS-1846201

Title: Serotonergic innervation of the nucleus accumbens and ventral pallidum are highly conserved among primates.

Authors: *H. N. SMITH[1], D. N. JONES[2], E. L. MUNGER[1], P. R. HOF[3], C. SHERWOOD[4], M. RAGHANTI[1];
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Abstract: Serotonin is a phylogenetically ancient substance thought to regulate change in behavior and emotion over time through its actions in the brain's reward pathway. Modulating impulsivity, patience, and behavioral inhibition, serotonin affects behaviors such as personality style and sociability, which may buffer the emotional impact of group living. Humans and apes are known to have more serotonin than monkeys in the dorsal and medial caudate nucleus and dorsal putamen, contributing to the ability to select appropriate social interactions. The current study builds on earlier results by examining serotonergic axon innervation density in two important nodes in the reward system: the nucleus accumbens (NAcc) and ventral pallidum (VP). The present sample included humans (n = 6), bonobos (n = 4), chimpanzees (n = 6), gorillas (n = 4), olive baboons (n = 6), moor macaques (n = 6), Japanese macaques (n = 6), pigtailed macaques (n = 6), rhesus macaques (n = 6), capuchin monkeys (n = 6), owl monkeys (n = 4), tamarins (n = 6), and marmosets (n = 6). All individuals were adult and free of neuropathological alterations. Brain sections were immunohistochemically processed for serotonin transporter (SERT) (Millipore, MAB 5618), and stereological methods (Optical Fractionator and SpaceBalls probes, MBF Bioscience) were used to quantify the length density of SERT-immunoreactive axons and neuron densities from adjacent Nissl-stained sections. An Independent-samples Kruskal-Wallis test was used to evaluate differences of SERT-immunoreactive axon densities normalized by neuron densities among species in both brain regions. No differences among species were detected in the NAcc ($H(11) = 16.8$, $p = .114$). A species difference was detected in the VP ($H(11) = 30.7$, $p = .001$). Pairwise comparisons with adjusted p-values showed that moor macaques had higher innervation than owl monkeys ($p = .033$), marmosets ($p = .031$), and capuchins ($p = .047$). Moor macaques are considered an 'egalitarian' species and are isolated on the island of Sulawesi, Indonesia. More research needs to be done to explain their unique features. Based on the current results, the serotonergic system in the nucleus accumbens and ventral pallidum appears to be evolutionarily conserved among primate species, suggesting innervation levels that provide a baseline function to support social behavior. Funding: NSF BCS-1846201

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Poster

PSTR290. Motivation, Reinforcement, and Reward

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.05/NN8

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIMH IRP

Title: Automated home-cage cognitive testing system for marmosets

Authors: *H. E. HARKINS, K. CHRISTOPHER, D. MATROV, I. INGRAM, Y. CHUDASAMA;
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Abstract: The common marmoset (*Callithrix jaccus*) represents a primate species of growing interest in cognitive-behavioral research largely due to their potential for study with optogenetic and related methods that are routinely applied to the brains of rats and mice. Similar to humans, marmosets live in close-knit families with a high degree of cooperative care and learn through social and vocal interactions. They also provide the advantage of being small, thereby reducing the need for large enclosures. In addition, critical features of the primate brain, such as the prefrontal cortex, hippocampus and thalamus, and their connections, are shared between the marmoset and more studied primates such as the Old-World macaque (Kaas, ILAR J. 2020; 61:260-273) and humans (Chaplin et al., J Neurosci. 2013; 33:15120-5). Thus, from the perspective of behavioral neuroscience, the marmoset represents an exceptional model of human cognition.

Many behavioral studies have used touchscreen operant platforms to examine high order cognitive functions (e.g., Clarke et al. Science. 2004; 304: 878-880). Typically, these tests are conducted in isolation, to enable experimental control while preventing distraction from the family unit. However, due to their social nature, marmosets prefer to be in close proximity to their family, and under these conditions, they work reliably over long time periods. With this in mind, some researchers have supported home-cage testing equipment (e.g., Takemoto et al., J. Neurosci. Methods. 2011; 199:82-86). Here, we report a novel, custom designed automated behavioral control testing system to assess complex cognitive-executive functions in freely behaving marmosets. The testing chamber, fitted with a touchscreen, stimulus lights, and food dispensers, was attached to the home-cage, and the monkeys could freely enter and exit as they pleased. Once habituated to the test box, monkeys worked for up to 3 hours completing many hundreds of trials (range 150-450). This approach, we found, allowed marmosets to work at their own pace and develop self-motivation to learn the task.

Thus far, we have trained 4 monkeys on a simple discrimination task in which two different stimuli were presented on the touchscreen. Touching the correct stimulus was rewarded with banana milkshake. The marmosets successfully attained over 80% accuracy in an average of 6 days (range 2-10) with fast response (2-5 s) and reward collection (< 3 s) latencies. Here, we report preliminary data on the effects of cholinergic manipulations on cognitive function using our home-cage behavioral control testing system.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

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Program #/Poster #: PSTR290.06/NN9

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH MH115874
NIH MH123993
NIH MH108665

Title: Roles of the nociceptin/orphanin FQ receptor in reward-related behaviors in mice

Authors: E. VAN DER RIJN[1,2], G. LIU[1,4], A. MERADIAN[1,4], A. PASQUALINI[1,4], M. A. ZAMBRANO[1,4], S. P. BROTHERS[5], K. J. RESSLER[1,3], *J. SUH[1,3];
[1]McLean Hosp., Belmont, MA; [3]Psychiatry, [2]Harvard Med. Sch., Belmont, MA; [4]Northeastern Univ., Boston, MA; [5]Univ. of Miami, Miami, FL

Abstract: The neuropeptide orphanin FQ/nociceptin receptor (NOR), the fourth member of the opioid receptor family, is widely distributed throughout multiple brain regions, including the amygdala. Although the NOR shares significant sequence homology with classic opioid receptors, emerging evidence suggests that the NOR system is involved in an anti-opioid action that suppresses the motivational effects of food and addictive substances such as alcohol. However, little is known about how NOR contributes to reward-related consummatory and seeking behaviors. To address this, we employed a battery of behavior tests combined with systemic administration of a non-peptide, brain-penetrant NOR agonist, SR-8993. To determine the effect of SR-8993 on consummatory behaviors, we first subjected male and female wild type adult C57BL/6 mice to a home cage binge-like drinking paradigm, Drinking in the Dark. We found that SR-8993 administration at doses of 1.0 and 3.0mg/kg BW significantly decreased both 20% ethanol (EtOH) and evaporated milk consumption. Next, we also investigated if SR-8993 affects seeking behaviors. In separate cohorts of mice subjected to EtOH conditioned place preference, we found that mice injected with SR-8993 (3.0 mg/kg BW) spent less time in EtOH-paired compartment during choice-test. In addition, we measured milk-seeking behaviors using Pavlovian and instrumental conditioning paradigms. We found that administration of SR-8993 at a dose of 1.0 mg/kg BW attenuated the number of pre-reward anticipatory nose-pokes responding to tone-cue in high performers in a Pavlovian conditioning task. Interestingly, in the instrumental conditioning task, SR-8993 at all doses did not significantly reduce milk seeking, yet 1.0 and 3.0 mg/kg BW both increased seeking behavior one day after the administration of SR-8993. Finally, we investigated if SR-8993 can alter behavioral structures including locomotion in an open field using Motion Sequencing (MoSeq), an unsupervised machine learning-based behavioral analysis method. Although MoSeq successfully parsed behavioral differences and similarities, we found that SR-8993 did not appear to affect stereotyped behaviors. In sum, these findings suggest that the NOR system is involved in consummatory and seeking behaviors, yet it appears to contribute to these behaviors in a dose-dependent, relatively selective manner, which depends upon the structure of tasks. Our results provide evidence that the NOR system may present promising targets for the development of novel pharmacotherapies for the treatment of alcohol use and eating disorders.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.07/NN10

Topic: F.04. Neuroimmunology

Support: Busch Biomedical Grant

Title: Increased persistence for reward seeking in mice lacking NOP the receptor for nociceptin

Authors: *M. NISSENBAUM[1], S. WALPOLE[1], V. SOTIROV[1], D. HU[1], J. E. PINTAR[2], A. W. KUSNECOV[1];
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Abstract: The Nociceptin/Orphanin FQ (N/OFQ) precursor propeptide is linked to reward-seeking, and the nociceptin receptor (NOP) has been shown to oppose behavioral deficits due to inflammation. Here we report in 3-5 month old NOP-deficient (NOP KO) and wildtype (WT) mice the effects of the immune stimulus LPS on operant responding in a progressive ratio schedule (PR), as well as effects on cognitive flexibility. NOP KO (20F; 35M) and WT (18F; 30M) mice on a C57BL/6 background were trained to nose poke into a trough that lifted a liquid dipper containing a 4% sucrose reward. After successful training under FR1 and FR3 schedules, mice were subjected to a PR schedule for three sessions. At 90 mins before PR testing on day 2, mice were injected IP with saline or LPS at a high (200µg/kg) or low (40µg/kg) dose. One more PR day followed without further treatment. Subsequent to this, mice were entered into a second phase (Phase 2) of operant training, that involved a rule change, such that an adjacent operandum needed to be nose poked to activate the liquid dipper. This rule-change for receipt of reward was designed to assess the lingering effects of LPS on cognitive flexibility. RESULTS: Prior to LPS exposure, NOP KO mice showed more persistent nose poking throughout the PR task when compared to WT controls. In females, there was an interaction of genotype x time (RM 2-way ANOVA $F_{(59, 1593)}$ $p=0.0045$), but no interaction for males, only genotype and time main effects (RM 2-way $p=0.0012$ and $p=0.0001$, respectively). Therefore, NOP KO mice demonstrated increased motivation to seek reward. In response to high and low LPS doses, responding was reduced regardless of genotype or sex ($p<0.0001$). In the saline treated group, the persistent responding in NOP KO mice was maintained. To test for lingering sickness or a learned aversion, the progressive ratio task was repeated 24h later (day 3 of PR), and NOP KO mice previously given LPS showed significantly greater recovery and responding compared to WT-LPS controls ($p=0.02$). This suggests that NOP may be needed to dampen post-inflammation pursuit of reward. These mice were then given an alternate rule to obtain reward (Phase 2). An efficiency quotient was calculated to determine how well mice learned the new task. Interestingly, while all groups learned the new task, females previously given LPS had slightly

higher efficiency rates than saline controls regardless of genotype (p=0.06). Both LPS-treated and saline treated NOP KO males had higher efficiency compared to WT controls (p<0.005). These data suggest that the N/OFQ system, and NOP stimulation particularly, may modulate reward seeking and cognitive flexibility in a sex-dependent manner.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.08/NN12

Topic: G.02. Reward and Appetitive Learning and Memory

Support: University of Delaware Research Fund
Delaware Center for Neuroscience Research COBRE P20 GM103653

Title: Implications of Birth Route on Reward-Mediated Behavior in Adult Prairie Voles

Authors: ***K. ROGERS**[1], M. PARTIE[2], E. KIERNAN[2], N. FOLEY[2], W. M. KENKEL[2]; [1]Psychological and Brain Sci., Univ. of Delaware Grad. Program In Behavioral Neurosci., Newark, DE; [2]Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Accumulating evidence from clinical studies on the long-term impact of Cesarean delivery (CS) has found increased risk in offspring for developing obesity later in life. We have examined this using prairie voles and find that CS offspring weigh more across development compared to vaginally delivered (VD) counterparts. In this study, we explored the impact of CS on dopamine and reward-mediated behavior as a potential mechanism of increased weight gain. We used a conditioned place preference (CPP) paradigm and operant conditioning schedules to assess learning and motivation in adult prairie voles. Preliminary results from the CPP testing suggests the efficacy of sucrose does not differ between CS and VD voles when assessing context-dependent reward learning [$F(1, 13) = 0.004$, $p = 0.952$]. However, CS offspring demonstrate stronger acquisition of the FR1 schedule ($M = 38.8$, SD = 4.32; $M = 25.75$, SD = 13.96) measured by responses for an appetitive stimulus. To assess the role of DA in behavioral outcomes of CS, we intend to include analysis of tyrosine hydroxylase in the reward and appetite-regulating brain regions compared to VD offspring. These results will help us better understand the neurodevelopmental consequences of CS on dopamine and reward-mediated behavior as a potential mechanism for increased risk of obesity in adulthood.

Disclosures: **K. Rogers:** None. **M. Partie:** None. **E. Kiernan:** None. **N. Foley:** None. **W.M. Kenkel:** None.

Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.09/Web Only

Topic: G.02. Reward and Appetitive Learning and Memory

Support: UNAM-DGAPA- IN300321

Title: Discriminative properties of intracranial stimulation

Authors: *B. PACHECO GÓMEZ[1], W. ZEPEDA-RUIZ[1], D. VELAZQUEZ-LOPEZ[2], D. VELAZQUEZ-MARTINEZ[1];
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Abstract: Previous studies using electrical intracranial stimuli (ICS) as a discriminative cue, focused on estimating detection thresholds or on the discrimination between intensities. To our knowledge there is no direct comparison of the equivalence between variation of amplitude and variation of frequency on the discriminative functions. Seven Long Evans rats had an electrode aimed at the medial forebrain bundle (hypothalamus) and were trained to press a lever using a reinforcing intensity below motor alterations. Thereafter, rats were trained on a discrimination task where the previously used reinforcing ICS signaled a lever where a response was followed by sucrose reinforcer; on randomly alternating trials a -0.6 log ICS signaled an alternate lever where a similar response led to a reinforcer. After mastering discrimination, generalization tests were carried out varying intensity or frequency of ICS in ascending, descending or random order. Thereafter, rats had different doses of an apomorphine challenge while their intensity was varied in generalization tests. Rats learned the discrimination attaining discrimination indexes (DIs) of 90-98%. In generalization trials responding to the high-ICS was a function of the amplitude or frequency, but presentation order did not alter their DIs. After variations in the amplitude parameter, orderly generalization gradients were observed. Variations in the frequency parameter of ICS also produced orderly generalization gradients. Estimated DI_{50}s (expressed as charge of stimulation train) after frequency variations had a large coincidence with the DI_{50}s after frequency variations, in accordance with the counter model that posited that pulse frequency and amplitude of the stimulation train may be a tradeoff to determine the reinforcing properties of ICS. Although there is ample evidence of the involvement of DA receptors in the reinforcing properties of ICS, present results with apomorphine (that did not affect the generalization gradient after amplitude variations) and previous reports using DA antagonists indicate that administration of DA agents may be able to dissociate the reinforcing and discriminative properties of ICS.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.10/NN13

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Melanin-concentrating hormone (MCH) receptor 1 mediates increased sucrose reward driven by opioid activation of the nucleus accumbens in female rats

Authors: *Y. CAM, C. G. KOCUM, E. R. KONRAD, T. A. SCHWEIZER, T. K. HOUSKA, C. A. SARDINA, S. K. SURI, M. J. WILL;
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Abstract: Melanin-concentrating hormone (MCH) projections from lateral hypothalamus to nucleus accumbens (Acb) have been shown to mediate feeding behavior, yet this has not been characterized in terms of homeostatic vs. hedonic feeding processes. Hedonic feeding is driven by palatability, rather than energy deficit, and can be modeled through intra-Acb administration of the selective μ-opioid agonist D-Ala2, NMe-Phe4, Glyol5-enkephalin (DAMGO), which enhances motivation for palatable preferred diets. Pharmacological activation of MCH 1 receptors (MCH1R) within Acb has been shown to promote general feeding of chow in males but not in intact females. However, the effects of MCH on hedonic feeding have not been explored. Here, we investigated the effects of an MCH1R antagonist on DAMGO-induced operant responding for sucrose pellets in females. After bilateral intra-Acb cannulae surgery and a 7-day recovery period, rats were trained on a fixed ratio to respond to a lever for a sucrose pellet in operant test chambers. Then, animals were trained and tested under a progressive ratio operant task following intra-Acb administration of DAMGO (0μg and 0.25μg/.5μl/side) immediately following administration of MCH1R antagonist (N-(3-{1-[4-(3,4-difluoro-phenoxy)-benzyl]-piperdin-4-yl}-4-methyl-phenyl)-isobutyramide (SNAP-94847; 0μg, 1.5μg and 15μg/.5μl/side) in a counterbalanced fashion. As expected, DAMGO significantly increased breakpoint and active lever presses. SNAP-94847 had no influence on breakpoint, compared to vehicle, however, SNAP-94847 significantly reduced the breakpoint produced by intra-Acb DAMGO following both 1.5 and 15μg doses of SNAP-94847. The results of the study demonstrate that MCHR1 within the Acb may be a critical contributor to the opioid model of palatability-driven feeding in female rats.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.11/NN14

Topic: B.07. Network Interactions

Support: NIH grant R00 AA024215
NIH grant R01 AA028931
BBRF grant #27530

Title: Serotonin transients in the nucleus accumbens encode both appetitive and aversive stimuli

Authors: *R. WANG, T. JAMES, N. BALASUBRAMANIAN, C. MARCINKIEWCZ;
Dept. of Neurosci. and Pharmacol., Univ. of Iowa, Iowa City, IA

Abstract: The serotonergic (5-HT) circuitry from the dorsal raphe to the nucleus accumbens (NAcc) is involved in a variety of neural processes. But it remains elusive how 5-HT transmission in the NAcc changes in response to different sensory stimuli. In the present study, we expressed a 5-HT biosensor ($GRAB_{5\text{-}HT3.5}$) in the NAcc of male C57BL/6J mice via AAV infection, and performed wireless fiber photometry recordings while mice were being presented with different appetitive and aversive stimuli. First, when mildly food-deprived mice were offered palatable food (fruit loops) that they were previously familiarized with, we observed gradually increased fluorescent 5-HT transients in the NAcc, which remained elevated while mice were investigating the food but started to drop as food consumption began, suggesting that 5-HT transmission in the NAcc is associated with appetitive, but not consummatory, behavior. Interestingly, a small increase in NAcc 5-HT transients also emerged when mice were presented with the smell of the palatable food (from fruit loop fragrance oil) alone. Second, presentation of social stimuli, via a same-sex conspecific enclosed inside a corner cage in an arena, drove enhanced NAcc 5-HT transients, similar to the transients observed when mice were offered palatable food, indicating that 5-HT transmission in the NAcc encodes different appetitive stimuli with reinforcing values in a similar pattern. Finally, we assessed NAcc 5-HT response to aversive stimuli using an acute bright light exposure paradigm. In a dimly-lit (~ 20 lux) arena, a super bright white light (~1,800 lux) was unexpectedly illuminated, kept on for 2 min, and then turned off. We observed a sudden increase in 5-HT transients accompanying the bright light illumination, which sustained at the high level until lighting returned dim. During the elevation of NAcc 5-HT transients, fluorescent peaks with much greater amplitudes were also observed, suggesting the occurrence of synchronous cell firing upon acute stress exposure. In conclusion, 5-HT transmission in the NAcc encodes both appetitive and aversive stimuli, which drive enhanced 5-HT transients that may entail different neural processes. Our findings could help better understand the role 5-HT plays in the NAcc.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.12/NN15

Topic: G.02. Reward and Appetitive Learning and Memory

Support: JTF Grant 61911
Sponsored by a grant from the Supporting Structures: Innovative Partnerships to Enhance Bench Science at CCCU Member Institutions

Title: Nmda receptor inhibition on rodent optimal decision-making in the diminishing returns task

Authors: *S. D. FOUST, M. MAINS, H. ABOUEICH, B. WELLS, B. GOH, H. DOBLE, E. MCCURRY, E. SANCHEZ, G. DELICH, E. JANCOLA, E. DAUGHERTY, P. M. BAKER; Psychology, Seattle Pacific Univ., Seattle, WA

Abstract: There has been growing interest in using N-methyl-D-aspartate (NMDA) receptor antagonists as treatments for mood disorders, but there is still much to learn about their cognitive effects. Specifically, some have reported impairments in working memory while foraging behavior remains intact. Others have demonstrated changes in choice behavior related to delay or risk in operant tasks. Research has shown NMDA receptors can affect decision-making, and the antagonist MK-801 has been found to have varying effects in rodents. We investigated the role of NMDA receptors in the specific paradigm of optimal decision-making to further confirm the effects of MK-801 and to explore whether inhibiting NMDA receptors alters optimal decision-making processes. The Diminishing Returns task (DRT) has been used to measure this process with rats placed in a chamber containing two levers that return a sugar pellet reward after a delay. One lever has a fixed delay (FD) that returns a reward after 10 s. The other lever has a progressive delay (PD) that increases by 1 s after each press starting at 0 s. The task includes two conditions: no reset and reset. In the no reset condition, pressing the PD lever continuously increases its delay. In the reset condition, the delay of the PD lever can be reset to 0 s by pressing the FD lever. In both conditions, there is an optimal response rate on the PD lever that returns the most rewards at the least amount of delay in a session. 12 male and 12 female Sprague Dawley rats aged 2 - 4 months were each injected with 3 doses of MK-801 (0.06 mg/kg, 0.1 mg/kg, 0.2 mg/kg) and saline as the control on a counterbalanced schedule before testing in the DRT. Their lever choices were analyzed with generalized linear mixed models for effects of the treatments and sex of the rats and were compared to optimal values. We hypothesized MK-801 would diminish the ability to make optimal decisions. In the no reset condition, rats on the 0.2 mg/kg dose made significantly more choices for the PD lever than the FD lever compared to the other treatments (56.9% ± 4.8%, n = 14). In the reset condition, females made significantly more PD lever presses than males after receiving saline (females: 93.8% ± 1.1%, males: 88.7% ± 1.8%, n = 24). It was found that males and females on the 0.2 mg/kg dose made more optimal sequences of lever choices (females: 3.38 ± 0.87, males: 6.48 ± 1.67, n = 16). These results reveal a complex effect of both sex and NMDA receptor effects on optimal foraging behaviors and overall task responsiveness. Therefore, the findings suggest inhibiting NMDA receptors may not detrimentally affect the cognitive mechanisms involved in optimal decision-making as it is measured in this task.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.13/NN16

Topic: G.02. Reward and Appetitive Learning and Memory

Support: Mercer University Seed Grant

Title: Palatable food seeking following the selective Norepinephrine neurotoxin DSP-4 in rats after forced abstinence

Authors: L. N. CALLAN[1], J. M. BELFLOWER[1], J. T. BELFLOWER[1], G. LEE[1], C. V. KASE[1], A. D. PATEL[1], *A. GHEIDI[2];
[2]Biomed. Sci., [1]Mercer Univ., Macon, GA

Abstract: A growing body of literature suggests that food seeking/taking and drug addiction overlap in neurobiology. For instance, many drugs of abuse, as well as palatable foods, recruit cortical neuronal ensembles. Unknown, however, is how neuromodulators, such as norepinephrine (NE) from the Locus Coeruleus (LC), perturb medial prefrontal cortex (mPFC) neuronal ensembles, and food-seeking. To investigate the relationship between food seeking, neuronal ensembles, and NE, female rats were required to lever press (FR1) for banana-flavored sugar pellets for ten days. To minimize stress to the animals, they were not weighed and lavaged (to determine the estrus cycle) until day 6 of the study. On day 10 of sugar pellet self-administration, the rats were injected with the selective Norepinephrine neurotoxin DSP-4 (50 mg/kg/.i.p) or saline and placed in home cages for ten days. On day 20, rats were given a single re-exposure session to the self-administration context (without sugar pellet delivery). Their responses were recorded for one hour. One and half hours following the start of this re-exposure session, rats were transcardially perfused, and the mPFC was sectioned for dual immunofluorescence (IF) for the immediate early gene Fos and dopamine beta-hydroxylase (DβH) (for confirmation of NE loss). Our preliminary results show comparable levels of lever pressing and body weight in female rats given saline or DSP-4. We are now replicating with male rats, analyzing the female estrus cycle, and performing IF in mPFC sections.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.14/NN17

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA Intramural Funds ZIA DA000493
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Title: Unique pharmacodynamic properties and low abuse liability of the μ-opioid receptor ligand (S)-methadone

Authors: *M. R. LEVINSTEIN[1], P. A. DE OLIVEIRA[2], N. CASAJUANA-MARTIN[5], C. QUIROZ[2], R. C. BUDINICH[3], R. RAIS[6], W. REA[2], E. VENTRIGLIA[3], N. LLOPART[7], V. CASADÓ-ANGUERA[7], E. MORENO[7], D. WALTHER[4], G. C. GLATFELTER[4], D. WEINSHENKER[8], C. A. ZARATE, Jr.[9], V. CASADÓ[7], M. H. BAUMANN[4], L. PARDO[5], S. FERRE[2], M. MICHAELIDES[3,10];
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Abstract: (R,S)-methadone ((R,S)-MTD) is a μ-opioid receptor (MOR) agonist comprised of (R)-MTD and (S)-MTD enantiomers. (S)-MTD, thought to be the opioid inactive isomer, is being developed as an antidepressant and is considered an N-methyl-D-aspartate receptor (NMDAR) antagonist. Here we compared the pharmacology of (R)-MTD and (S)-MTD using in vivo, in vitro, and in silico methods. Broad receptor screening identified MOR as the main target for (R)-MTD and (S)-MTD. We use receptor occupancy autoradiography to show that racemic and both enantiomers ((R,S)-MTD: 4 mg/kg; (R)-MTD: 2 mg/kg; (S)-MTD: 30 mg/kg) produce near total occupancy MOR (over 90% for (R,S)-MTD and (R)-MTD and over 75% for (S)-MTD) at pharmacologically relevant doses. Additionally, we demonstrate here that, at these same doses, none of these drugs interact with NMDARs in vivo. Moreover, we performed [^{35}S]GTPγS and find that (R,S)-MTD, (R)-MTD, and (S)-MTD activate MORs, though (R)-MTD is the most potent. Using the hot plate assay, (R,S)-MTD (EC_{50}: 1.2 mg/kg), (R)-MTD (EC_{50}: 0.5 mg/kg), and (S)-MTD (EC_{50}: 17.9 mg/kg) produce full analgesia in rats. We next performed intravenous self-administration in rats and found that unlike (R,S)-MTD and (R)-MTD, (S)-MTD is a weak reinforcer. Additionally, (S)-MTD failed to induce locomotor stimulation in mice or to affect extracellular dopamine in the ventral tegmental area of rats. Furthermore, (S)-MTD antagonized motor effects of (R)-MTD. In bioluminescence resonance

energy transfer assays in transfected HEK-293 cells, (R)-MTD acted as a full efficacy agonist at MOR and the MOR-galanin$_1$ receptor heteromer (MOR-Gal$_1$R). By contrast, (S)-MTD acted as a partial agonist at MOR, with complete loss of efficacy at MOR-Gal$_1$R, a key mediator of the dopaminergic effects of opioids. We then utilize computer modeling to propose a novel molecular mechanism underlying the MOR-Gal$_1$R heteromer-dependent effects of (S)-MTD which will be useful in future drug development. Collectively, our results demonstrate that (S)-MTD is a novel prototype opioid with minimal abuse liability, most likely due to its lack of activity at MOR-Gal$_1$R sites mediating reinforcing effects of opioids.One-sentence summary (S)-MTD, like (R)-MTD, binds to and activates MORs in vitro, but (S)-MTD antagonizes the MOR-Gal$_1$R heteromer, decreasing its abuse liability.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.15/NN18

Topic: G.02. Reward and Appetitive Learning and Memory

Support: PAPIIT Grant IA206521
PAPIIT Grant IN227123

Title: Muscarinic receptors in the basolateral amygdala act in synergy to impinge a hedonic value related to taste experience.

Authors: *E. RODRÍGUEZ NAVA[1], V. TORRES GARCÍA[2], R. ALCANTARA RIVAS[2], G. ROLDÁN ROLDÁN[3], O. PICAZO PICAZO[1], J.-P. MORIN[2];
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Abstract: The basolateral amygdala (BLA) is a functionally heterogeneous brain area that encodes and stores valence-related information (Beyeler et al., 2018; Kim et al., 2016). This structure receives dense projections from the basal forebrain cholinergic system (Alexander J. McDonald, 2020), where its abundant muscarinic receptors (A. J. McDonald & Mascagni, 2011; Alexander Joseph McDonald & Mascagni, 2010) are thought to promote neuronal plasticity mechanisms underlying emotional learning and memory (Crouse et al., 2020). The attenuation of neophobia (AN) is an incidental type of taste learning in which the initial hesitation in ingesting a novel taste, due to a lack of knowledge regarding its post-ingestive consequences, attenuates upon repeated presentations (Chinnakkaruppan et al., 2014; Reilly & Bornovalova, 2005). Under laboratory conditions, in murine models, this is observed by an augmented intake of a taste as well as increased palatability (Lin et al., 2012), indicating that a valence switch occurs during the task. In the present study, we theorized that muscarinic receptor antagonism in the BLA, by bilateral microinfusions of scopolamine (SCOP) after novel taste presentation, would interfere with AN. As we showed previously (SfN 2022 poster 224.12), this treatment not only prevented AN but produced a robust aversion for the taste on subsequent presentations. We now present new data showing how intra-BLA SCOP infusions after novel taste affects taste palatability on the following day as showed by licking microstructure analysis. We also sought to determine whether this intra-BLA SCOP-induced taste avoidance was prone to latent inhibition by pre-exposing rats on four days before performing taste-paired scopolamine infusion on the fifth day. Here, a significant taste avoidance was produced as observed on the sixth day, albeit not as strong as when SCOP was administered after the novel taste. Moreover, specific M1-type or M3-type muscarinic receptor antagonism was performed after novel taste intake by intra-BLA microinfusions of pirenzepine or 4-DAMP, respectively. Although each treatment was able to prevent the increase in taste preference characteristic of the AN task -and observed in control animals-, they did not produce the strong avoidance that we observed with the SCOP treatment. Our data suggest that muscarinic receptors in the BLA work in synergy to impinge a hedonic value upon a taste experience, modulating the taste's valence upon subsequent encounters.

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Poster

PSTR290. Motivation, Reinforcement, and Reward

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Program #/Poster #: PSTR290.16/NN19

Topic: G.02. Reward and Appetitive Learning and Memory

Title: Injections of gastrin releasing peptide into the rat medial nucleus accumbens cause a transient inhibition of the intake of a sweetened fat diet

Authors: *W. E. PRATT, R. B. COCHRAN, S. CHUANG, E. IRVIN, S. PATEL, L. WILSON;
Dept. of Psychology, Wake Forest Univ., Winston Salem, NC

Abstract: Gastrin releasing peptide (GRP) is a neuropeptide that is released in the gut following food ingestion. It has many peripheral digestive functions, such as stimulating gastrin release, regulating pancreatic secretions, and increasing gastrointestinal motility. Like many other gut-associated peptides released in response to energy metabolism, GRP has receptors distributed throughout the brain (Wolf & Moody, 1985). This includes heavy expression of its receptor within the hypothalamus and nucleus accumbens. These regions are involved in regulating food intake in response to energy deficit and the hedonic value of palatable foods. In the current experiments, we examined whether GRP injection into either the nucleus accumbens or paraventricular nucleus of the hypothalamus could affect intake of a sweetened fat diet. Two groups of male Sprague-Dawley rats were implanted with bilateral guide cannulas aimed at either the paraventricular nucleus of the hypothalamus (N = 6) or the medial nucleus accumbens shell (N = 8). These non-restricted animals were then habituated to daily 2-hr access of a high fat/sucrose diet consisting of 10% sugar in vegetable shortening. Diet intake, water intake, and locomotor measures were monitored throughout each session. Upon habituation to the diet and injection procedures, each rat received bilateral intracranial injections of 0, 100, 200, and 300 ng GRP/side in 0.5 microliters of isotonic saline directly into the paraventricular nucleus or the nucleus accumbens immediately prior to being placed into the feeding chambers. Each rat received all doses of GRP in a random order across multiple experimental days. Consistent with past research examining the effects of GRP on food intake when administered systemically or into the amygdala (e.g., Fekete et al., 2002; Ladenheim et al., 2002), GRP infusion into the nucleus accumbens caused a short-lived reduction in consumption of the sweetened fat diet early in the first hour of each session [effect of GRP: F (3,21) = 5.00, p = 0.009; GRP X time interaction: F (33,231) = 2.96, p = <0.001]. A similar trend was observed following injections into the paraventricular nucleus of the hypothalamus, although the inhibition did not achieve significance [effect of GRP: F (3,15) = 2.59, p = 0.091. GRP X time interaction: F(33,165) = 1.48, p = 0.06]. These data show, for the first time, that GRP may function to transiently impact the intake of palatable diets through actions within the nucleus accumbens and associated circuitry.

Disclosures: W.E. Pratt: None. **R.B. Cochran:** None. **S. Chuang:** None. **E. Irvin:** None. **S. Patel:** None. **L. Wilson:** None.

Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.17/NN20

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIDA Grant F31DA057817
NIDA Grant R01DA043533

Title: Cannabinoid receptor-1 signaling promotes sensitivity to devaluation in male, but not female, sign-tracking rats.

Authors: *C. A. STAPF[1,2], S. E. KEEFER[3], J. M. MCINERNEY[2,3], D. J. CALU[3];
[1]Neurobio., Univ. of Maryland, Baltimore, Baltimore, MD; [2]Program in Neurosci., [3]Dept. of Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Sign-tracking rats are insensitive to outcome devaluation but become devaluation sensitive after extended Pavlovian lever autoshaping (PLA) training. However, this finding was established using only male rats. Female rats are more likely to sign-track and show increased lever pressing compared to male rats, suggesting they may be less sensitive to devaluation even after extended training. Cannabinoid-1 receptor (CB1R) signaling in the dorsomedial striatum (DMS) regulates instrumental outcome devaluation suggesting this system may also be important for devaluation of Pavlovian behaviors like sign- and goal-tracking. To understand the contribution of DMS CB1R signaling to sex- or tracking-specific responses in outcome devaluation, we performed intracranial infusions of the CB1R inverse agonist, rimonabant, in the DMS before reinforced PLA sessions and outcome devaluation test sessions. We used a within-subject satiety-induced outcome devaluation procedure in male and female rats after extended training in PLA. We sated rats on training pellets (devalued) or home cage chow (valued) then tested rats in nonreinforced PLA sessions. During outcome devaluation tests, male sign-tracking rats were sensitive to devaluation while female sign-tracking rats were not. Inverse agonism of CB1Rs in the DMS with rimonabant reversed devaluation sensitivity in male sign-tracking rats. We saw no effect of DMS rimonabant injections on tracking behaviors during reinforced PLA sessions. Together, our results demonstrate that dorsal striatal endocannabinoid signaling has sex-specific effects on the devaluation sensitivity of Pavlovian behaviors in male and female rats.

Disclosures: C.A. Stapf: None. **S.E. Keefer:** None. **J.M. McInerney:** None. **D.J. Calu:** None.

Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.18/OO1

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R25NS080686
NIH Grant MD007599

Title: Methamphetamine Induces Conditioned Place Preference in a Sex and Strain Specific Manner in Adolescent Mice.

Authors: *L. NUNEZ SEVERINO[1], A. B. TOUSSAINT[2], G. MCKENNA[1], N. S. BURGHARDT[1,3];
[1]Psychology Dept., Hunter College, CUNY, New York, NY; [2]Zuckerman Inst., Columbia Univ., New York, NY; [3]Behavioral and Cognitive Neurosci., The Grad. Center, CUNY, New York, NY

Abstract: There are sex differences in the use and response to methamphetamine, with women initiating use earlier and transitioning to regular use faster than men. However, studies investigating the cellular basis of addiction often only test male rodents during adulthood. We used a conditioned place preference (CPP) paradigm to test whether there are sex differences in the rewarding effects of methamphetamine (1mg/kg) in mice of two strains (C57Bl/6 and 129Sv/Ev). CPP training began during adolescence (postnatal day 41), which is usually when substance abuse is initiated in humans. To evaluate the neural basis of methamphetamine-induced CPP, mice were perfused 90 minutes after the CPP test (drug-free) and immunohistochemistry was used to label cells expressing the neural activity marker c-Fos. Behaviorally-induced expression of c-Fos was quantified in the core and shell of the nucleus accumbens (NAc) using ImageJ software. In the C57Bl/6 strain, we found that methamphetamine only induced CPP in females ($n = 12$/group, $p < 0.05$), effects that were associated with increased c-Fos-positive (+) cells in the NAc shell ($n = 10$/group, $p = 0.05$**)**. Interestingly, when C57Bl/6 mice were on drug, methamphetamine stimulated locomotor activity in both sexes, with neither sex exhibiting locomotor sensitization. In the 129Sv/Ev strain, methamphetamine only induced CPP in males ($n = 12$/group, $p < 0.01$), which was also associated with an increase of c-Fos+ cells in the NAc shell ($n = 8$, $p < 0.05$). Overall, the effects of methamphetamine on locomotor activity were less dramatic in the 129Sv/Ev strain than the C57B/6 strain. In 129Sv/Ev mice, methamphetamine failed to increase locomotion in either sex until the fourth injection and sensitization was only detected in males ($p<0.01$). These findings clearly demonstrate sex and strain differences in the response to methamphetamine and are consistent with existing literature indicating that the NAc plays a pivotal role in driving the rewarding effects of drugs of abuse.

Disclosures: L. Nunez Severino: None. **A.B. Toussaint:** None. **G. McKenna:** None. **N.S. Burghardt:** None.

Poster

PSTR290. Motivation, Reinforcement, and Reward

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.19/OO2

Topic: D.07. Visual Sensory-Motor Processing

Title: Sensory-motor system and reinforcement learning

Authors: *Y. KYUNG, S.-L. KIM;
Yonsei Univ., Seoul, Korea, Republic of

Abstract: Reinforcement learning is a prominent and systematic technique in machine learning that involves deliberately modifying an agent's actions. By leveraging the agent's responses to the environment, it gradually improves its decision-making capabilities. However, traditional reinforcement learning models have limitations in capturing the intricate nature of sensory motor mechanisms. To address this challenge, we propose a novel framework grounded in statistical theory and control theory, aiming to overcome these limitations. Our framework incorporates the formulation of a cost function for action selection, serving as the foundation for developing an algorithm that estimates rewards and discount factors using biological data. This estimation process enables more precise predictions of escape behaviors. Moreover, our neuroscience-inspired model offers a strategic approach to decompose complex tasks into independent decision modules, facilitating the training of an artificial agent capable of emulating biological escaping systems.

Disclosures: Y. Kyung: None. **S. Kim:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.01/OO3

Topic: G.03. Motivation

Support: Littlefield and Ransom Fellows Grant

Title: Dose-dependent effects of oral hormonal contraceptives on female gonadal function and amphetamine extinction.

Authors: *A. VASQUEZ, G. KIM, J. M. DOMINGUEZ, M. H. MONFILS, H. J. LEE; Univ. of Texas At Austin, Austin, TX

Abstract: Women are at an increased risk for developing substance use disorder (SUD), in part due to fluctuating levels of gonadal hormones, such as estradiol and progesterone, during the menstrual cycle. A common type of treatment for SUD in women is exposure therapy—an approach largely based on extinction. Changes in gonadal hormone levels across the menstrual cycle, as well as those induced by hormonal contraceptives (HC) among women of reproductive age, affect extinction, but are rarely considered. HCs work by suppressing hormonal fluctuations and levels of gonadal hormones in the body to prevent ovulation. Previous research in our lab has demonstrated that HC implants containing Levonorgestrel (LNG), a synthetic progestin commonly used in HCs, led to a rapid reduction in preference for amphetamine (AMPH)-associated context. Additionally, research on fear conditioning has shown that the timing of LNG administration may be important for extinction learning. The current experiment investigated whether oral administration of LNG, only during extinction, would lead to a reduction in AMPH-preference. Female rats underwent AMPH-conditioned place preference. They were then tested for their AMPH-preference either (1) over three sessions (ie., extinction learning sessions) while

receiving oral LNG (250µg/rat), or (2) during an estrous cycle stage associated with higher levels of gonadal hormones (i.e., proestrus/estrus). Both groups initially showed preference for the AMPH-associated context regardless of hormonal treatment. However, the LNG females showed no significant preference by the third extinction session, whereas naturally cycling females on proestrus/estrus stages still showed preference. Interestingly, estrous cycles of LNG females were not affected at the dose (250µg/rat) that influenced AMPH extinction. A higher dose (500µg/rat) of oral LNG still did not lead to persistent estrous stages associated with lower gonadal hormone levels (i.e., diestrus/metestrus), unlike what has been previously reported. Interestingly, uterine horn width, an index of prior exposure to high levels of estrogens, was significantly thinner in both high and low dose LNG rats as compared to proestrus/estrus rats, but not significantly different from diestrus/metestrus rats, suggesting that administration of the oral contraceptive was not without consequence. The findings are consistent with previous results from our lab and suggest a dose-dependent effect of LNG on gonadal function. Future work for this study will assess an optimal dose of LNG that leads to a persistent low gonadal hormonal state to assess conclusive effects of LNG on AMPH-extinction in females.

Disclosures: A. Vasquez: None. **G. Kim:** None. **J.M. Dominguez:** None. **M.H. Monfils:** None. **H.J. Lee:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.02/OO4

Topic: G.03. Motivation

Title: Relationship between attention behaviors and prefrontal-parietal EEG synchronization in rats during proestrus-estrus

Authors: *C. A. DOMÍNGUEZ-ESTRADA[1], E. HERNANDEZ-ARTEAGA[2], A. Z. GÓMEZ-MÉNDEZ[1], M. HERNÁNDEZ-GONZÁLEZ[1];
[1]Inst. de Neurociencias, Univ. de Guadalajara, Guadalajara, Mexico; [2]Facultad de Ciencias para el Desarrollo Humano, Univ. Autónoma de Tlaxcala, Guadalajara, Mexico

Abstract: Female rats display behavioral changes in response to differences in sex hormone levels that impact the functionality of certain brain areas, according to the stages of the estrous cycle. In this study, we characterized the electroencephalographic (EEG) activation and coupling between the medial prefrontal and posterior parietal cortices during antagonistic phases of the estrous cycle (proestrus-estrus vs. diestrous), as well as the attention that female rats paid to a sexually experienced male. The amount of nose pokes made while the rats were in a sexual incentive motivation box served as an index for the level of attention focused to the stimuli. Two situations—an awake-quiet state without a male rat present and an awake-quiet state with a male rat present—were used to record EEGs. The females displayed reduced latency with longer frequency and duration of nose pokes during proestrus-estrus. Regardless of the estrous cycle

phase, the females in both cortices presented increased absolute power in all EEG bands recorded in the presence of the male. Regardless of whether a male was present, the estrous females also showed higher EEG coupling between the medial prefrontal and posterior parietal cortices of the left hemisphere in all EEG bands. The greater attention focused to, and proper processing of the sexual signals released by the male may be related to the increased synchronization between prefrontal- parietal regions. Therefore, it is likely that a stronger functional connection between the prefrontal and parietal cortices is needed to display the proceptivity and receptivity behaviors that are specific of the proestrus-estrus phase.

Disclosures: C.A. Domínguez-Estrada: None. **E. Hernandez-Arteaga:** None. **A.Z. Gómez-Méndez:** None. **M. Hernández-González:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.03/OO5

Topic: G.03. Motivation

Title: Influence of prenatal stress on prefrontal-accumbens electroencephalographic correlation during the first sexual interaction in male rats

Authors: *A. Z. GOMEZ MENDEZ, P. CORTES ESPARZA, C. DOMÍNGUEZ ESTRADA, M. HERNÁNDEZ GONZÁLEZ;
Univ. de Guadalajara, GUADALAJARA, Mexico

Abstract: The first sexual interaction in male rats plays a vital role in the development of their sexual behavior. The conjunct activity of two specific brain regions, the medial prefrontal cortex (mPFC) and the nucleus accumbens (NAcc), appear to be involved in processing sexually relevant stimuli during the acquisition of sexual experience. Any alterations in these structures could have a negative impact on sexual behavior. Previous studies have indicated that prenatal stress can have detrimental consequences for the development of the mPFC and NAcc. These effects may persist into adulthood and hinder the acquisition of sexual experience, especially during the first sexual interaction in male rats. Considering the forementioned context, the objective of this study was to analyze the impact of prenatal stress on the electroencephalographic correlation (rEEG) between the mPFC and NAcc during the first sexual interaction in male rats. To conduct the study, a sample of 16 male Wistar rats was used, divided into two groups: one group experienced prenatal stress, while the other did not. From the time of weaning, the male rats were exclusively housed with other males and were not exposed to female rats. At 90 days of age, the rats underwent surgery to bilaterally implant electrodes in the mPFC and NAcc. EEG activity was recorded under two conditions: 1) during the first interaction with an ovariectomized (OVX) female, and 2) during the first interaction with a receptive female (RE). The results showed that rats of the prenatal stress group exhibited an increased susceptibility to changes in interhemispheric correlation. When in the presence of a receptive

female, rats in the prenatal stress group showed a higher correlation between the NAcc in the fast frequencies, while for the correlation between the mPFC, such an increase was observed in the theta band. In contrast, the stress-free group showed higher susceptibility in intrahemispheric correlation. The presence of a receptive female was associated with an increase in the correlation between the left mPFC and NAcc in the beta band. These findings suggest that prenatal stress has a differential impact on brain electrical activity during the first sexual interaction, which may have implications for both the neurophysiological and behavioral aspects associated with sexual behavior in male rats.

Disclosures: A.Z. Gomez mendez: None. **P. Cortes Esparza:** None. **C. Domínguez Estrada:** None. **M. Hernández González:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.04/OO6

Topic: G.03. Motivation

Title: Monitoring progression of motivated behaviors during models of chronic female stress

Authors: *M. MCGRAW[1], C. CHRISTENSEN[2], A.-J. LI[3], E. QUALLS-CREEKMORE[2]; [1]Washington State Univ. Grad. IPN, Pullman, WA; [3]Integrative Physiol. and Neurosci., [2]Washington State Univ., Pullman, WA

Abstract: Exposure to stress has been shown to dysregulate motivated behaviors; while chronic stress commonly results in decreased motivated behaviors, as seen in depression, motivation has also been shown to increase with mild stress exposure. The bidirectional response to stress is not well characterized, especially in females. Chronic social defeat (CSD) is the standard protocol for psychosocial models of stress in mice as it is translationally relevant to the daily social and relationship stressors we encounter. However, this model has historically excluded female mice due to the model's reliance on territorial aggression which is typically absent in female mice. Additionally, most studies assess motivation after the fact, potentially occluding changes in motivation throughout the progression from acute to chronic stress. Our study seeks to compare and validate two proposed chronic social stress protocols that accommodate female cohorts. Model one introduces both a male and female C57 intruder into the home cage of a male CD1 mouse (Chronic Non-discriminatory Social Defeat Stress, CNSDS) to induce indiscriminate attack behavior. Model two replaces territorial aggression with social crowding (Social Crowding Stress, SCS). A female C57 mouse is exposed to daily prolonged investigation, vocalizations, and general contact with 8 unfamiliar female CD1 mice. Motivated behavior of controls (N=10) and experimental mice (N=10) are continuously monitored via an in-home operant feeding device (FED3) that dispenses sucrose pellets for trained nose pokes. Following 10-15 days of stress, we will use the standard social interaction assay to establish successful defeat and evaluate whether mice were susceptible or resilient to the stressors. We hypothesize

that there will be an initial increase in motivated behavior during the initial exposure to stress as a potential coping mechanism. However, as variations in exact stressor intensity and perception of stress for each mouse will occur, we anticipate that some mice will experience an overall mild-moderate stressor and others will experience severe stress. Preliminary data suggests mild-moderate stress will progressively increase their motivated behaviors while a severe stressor will alternatively decrease their motivated behaviors over time, resulting in anhedonia. Further, we aim to identify if resilient and susceptible populations correlate with differences in motivated behavior. Together, this study promotes the continued effort to compensate for the lack of female research in behavioral studies, as well as beginning to investigate the bidirectional switch in behavior as a product of stress over time.

Disclosures: **M. McGraw:** None. **C. Christensen:** None. **A. Li:** None. **E. Qualls-Creekmore:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.05/OO7

Topic: G.03. Motivation

Support: R01 1R01AA029386-01A1 (HJL)

Title: Sex Differences in the Renewal of Alcohol Seeking Rats

Authors: *T. A. SIMMONS[1], M. H. MONFILS[2], H. J. LEE[3];
[1]Psychology, Univ. of Texas at Austin, Austin, TX; [2]Univ. of Texas At Austin, Austin, TX; [3]Univ. of Texas at Austin Dept. of Psychology, Austin, TX

Abstract: Environmental cues become conditioned stimuli when associated with alcohol consumption, and facilitate alcohol-seeking, even during abstinence, leading to relapse. The gradual weakening of a conditioned response, or extinction, can reduce cue-conditioned responses by exposing discrete alcohol cues without alcohol consumption; however, extinguished cue-conditioned alcohol-seeking responses often return under certain conditions. One such phenomenon is renewal when the cue is presented in a different context than the extinction context. Existing research suggests sex differences whereby males exhibit more robust renewal of both appetitive and fear responses (Anderson and Petrovich, 2015; Binette et al., 2022); however, the presence of sex differences in renewal of alcohol-seeking behavior is not known. In the current study, we investigated the impact of contextual shifts and discrete environmental cues on renewal of alcohol-seeking behavior in rats. Male (n=5) and female (n=8) Long-Evans rats first underwent an induction phase: 15% unsweetened alcohol was provided MWF on a 24-hour schedule over a 5-week period. Then, Pavlovian conditioning took place in context A (standard conditioning chamber) where a 20-second light presentation was paired with a 10-second presentation of sipper containing 15% unsweetened alcohol (8 trials/session, 12

daily sessions). Subsequently, extinction (12 trial/session, 12 daily sessions) and testing (4 trials) occurred in context B which consisted of
smooth flooring, lemon scents, and black wall on the front and back of conditioning chambers. A 20-second light presentation was paired with a 10-second presentation of sipper without alcohol. Renewal testing (4 trials) occurred in context A. The results demonstrated successful extinction as measured by low levels of sipper contact (indicating reduced alcohol-seeking behavior) during extinction memory recall in context B. Notably, rats showed an overall increase in sipper contact when placed back in the original alcohol associated context (context A). While the renewal effect was only significant in males and not in females a larger cohort is needed to yield meaningful effect size estimates. Further research is warranted to explore potential factors contributing to the lack of renewal in females, including variability in the estrous cycle.

Disclosures: T.A. Simmons: A. Employment/Salary (full or part-time):; The University of Texas at Austin. 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.; Hongjoo J Lee (1), Marie-H Monfils (1),Rueben A Gonzales (2). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIH R01 1R01AA029386-01A1 (HJL) . D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); N/A. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); N/A. F. Consulting Fees (e.g., advisory boards); N/A. Other; N/A. **M.H. Monfils:** None. **H.J. Lee:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.06/OO8

Topic: G.03. Motivation

Support: Swedish Research Council, VR project number 2018-02320 (to Eric Augier)

Title: The effects of prolonged social isolation in adulthood on alcohol-related behaviors in female and male Wistar rats

Authors: *A. COPPOLA, M. HEILIG, E. AUGIER;
Linköping Univ., Linköping, Sweden

Abstract: Social exclusion has been associated with the vulnerability to develop alcohol-use disorders in humans. However, how impoverished social conditions promote addictive behaviors is understudied and most preclinical works focus on rodent models in non-operant settings, that do not fully reflect the behavioral complexity of the human condition. We therefore aimed to investigate the role of social isolation in alcohol-related behavior using a rat model of operant

self-administration. For this purpose, we screened adult male (n = 32) and female (n = 32) Wistar rats for interindividual differences in a battery of alcohol-related behaviors, including choice of alcohol over a sweet reward and punishment-resistant alcohol drinking. Following this, animals were either individually housed or maintained group-housed for the rest of the experiment (n = 16 per group per each sex) and the effect of housing conditions on these alcohol-related behaviors was assessed. Behavioral screening indicated sex differences, with males being more motivated for alcohol than females ($p < 0.001$) but females being more resistant to contingent punishment than males ($p < 0.01$), despite equal intake of alcohol in unpunished conditions. However, we found no significant effect of prolonged social isolation at adulthood on any of the alcohol-related behaviors tested, in either male or female rats. Future studies will be required to assess whether social isolation at earlier developmental ages could instead affect addiction-like behavior in rats.

Disclosures: **A. Coppola:** None. **M. Heilig:** None. **E. Augier:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.07/OO9

Topic: G.03. Motivation

Support: NIH T32AA007471
RO1 RO1AA029386

Title: Retrieval+extinction attenuates alcohol-seeking behavior in male and female rats previously exposed to chronic ethanol vapor

Authors: *M. OLVERA[1], M. RASKIN[2], R. U. COFRESI[3], R. GONZALES[4], M. H. MONFILS[5], H. J. LEE[6];
[1]Univ. of Texas at Austin, Austin, TX; [2]Univ. Of Texas At Austin Inst. For Neurosci., Univ. Of Texas At Austin Inst. For Neurosci., Austin, TX; [3]Psychological Sci., Univ. of Missouri, Columbia, Columbia, MO; [4]Univ. of Texas, Austin, TX; [5]Dept. of Psychology, Univ. of Texas At Austin, AUSTIN, TX; [6]Univ. of Texas at Austin, Dept. of Psychology, Univ. of Texas at Austin Dept. of Psychology, Austin, TX

Abstract: Environmental stimuli present during alcohol consumption can become conditioned cues that promote craving and relapse during abstinence. Extinction based therapy reduces conditioned response to the cue, but conditioned behavior may return under certain conditions. This may be due to the creation of a new competing inhibitory memory rather than modifying the original memory associated with cue. In contrast, the original memory may be modified if an extinction session is conducted after an isolated memory retrieval (retrieval+extinction; Ret+Ext) as initially shown with fear memory by Monfils et al., (2009). We recently showed that Ret+Ext was more effective than standard extinction (Ext) at reducing alcohol-cue reactivity in male rats

with moderate drinking history (Cofresi et al., 2017). In the current study, we tested the effectiveness of Ret+Ext using male rats (Experiment 1) and female rats (Experiment 2) with a history of alcohol dependence.Long-Evans rats were induced to drink 15% unsweetened ethanol (15E) on an intermittent 24hr schedule over 5 weeks. They then received chronic intermittent ethanol vapor (vapor group) over 10 days to induce physical dependence: controls received just air (air group). Rats were conditioned to associate a light cue with 15E delivered via a sipper over 12 sessions. They received one of two treatments, Ext or Ret+Ext, over 14 sessions. Lastly, rats were tested for return of alcohol seeking behavior in the presence of light alone (sipper site approach) and light with an empty sipper (sipper licks).Male and female rats that underwent Ret-Ext did not show significant return of sipper site approach regardless of their air or vapor exposure history (n=10-12 in each group). Rats that received Ext all showed significant return of sipper site approach with the exception of females in the air group (n=9-11 in each group). In the presence of an empty sipper, Ret-Ext was still effective at reducing sipper licks in male and female rats previously exposed to air or ethanol vapor. Among the rats that received Ext, only male rats showed significant return of sipper licks. This study replicated our previous work (Cofresi et al., 2017), which showed the effectiveness of Ret+Ext at reducing cue-reactivity in males with moderate drinking history, and now extended the findings to females. Importantly, we show that Ret+Ext can attenuate alcohol seeking behavior in male and female rats even with a history of alcohol dependence. Finally, our study suggests that Ext might influence alcohol seeking behavior (specifically sipper lick behavior) differently in male and female rats.

Disclosures: **M. Olvera:** None. **M. Raskin:** None. **R.U. Cofresi:** None. **R. Gonzales:** None. **M.H. Monfils:** None. **H.J. Lee:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.08/OO10

Topic: G.03. Motivation

Support: Swedish Research Council, VR project number 2018-02320 (to Eric Augier)

Title: Sex differences in pathological choice of alcohol over a healthy reward: role of GABAergic transmission in the CeA

Authors: *G. AUGIER, O. CONSOLER LYERE, L. XU, E. AUGIER;
CSAN, Linköping, Sweden

Abstract: Addiction leads to a progressively increased choice of drugs over healthy rewards. However, the choice of alcohol over alternative non-drug rewards has so far been largely overlooked as preclinical models of alcohol use disorder (AUD), and even less as a function of sex. We therefore aimed at investigating whether male and female rats would differ for choosing

alcohol over an alternative high-value reward and develop an addiction-like behavior. To address this issue, we applied a procedure in which about 15% of outbred male rats choose alcohol over an alternative high-value reward. We trained an equal number of male and female Wistar rats (n=32 per group) to self-administer a solution of 20% alcohol. Once stabilized, they were offered daily sessions of mutually exclusive choice between alcohol and 0.2% saccharin. We found that, although females tend to acquire 20% alcohol self-administration quicker than males during the first sessions of operant conditioning, males stabilized at higher levels of self-administration. While about 20 % of males chose alcohol over saccharin as previously observed, only about 8 % of females did. Importantly, alcohol choosing rats, whatever their sex, showed other traits reminiscent of clinical addiction, namely high motivation to obtain alcohol, and pursuit of alcohol despite adverse consequences. Finally, we investigated whether expression of the GABA transporter GAT-3 within central amygdala (CeA) was causal for alcohol choice over the sweet reward in females, as previously shown in male rats and translated to humans. For this, we injected independent groups of animals with an AAV-shRNAi targeting GAT-3, or a scrambled control vector, into the CeA and found that GAT-3 KD potently promoted pathological choice of alcohol over saccharin, and at an even higher extend in females. We finally assessed whether treatment with the $GABA_B$ PAM ADX71441 was able to reduce alcohol choice, as well as other alcohol-related behaviors in both male and females rats. All together, these results support a higher prevalence to develop addiction-like behaviors in male compared to female rats, which aligns with human epidemiological data. Furthermore, they indicate that decreased expression of GAT-3 within CeA is causal for pathological choice behavior in both sexes and that rescuing impaired GABA clearance due to suppressed GAT-3 expression might be a successful therapeutic mechanism in AUD.

Disclosures: G. Augier: None. **O. Consoler Lyere:** None. **L. Xu:** None. **E. Augier:** 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.; Eric Augier is PI of a research contract with Indivior Inc to evaluate novel candidates for AUD, which is not related to the present work.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.09/OO11

Topic: G.03. Motivation

Support: R01AA029386 (HJL)

Title: Alcohol consumption and alcohol seeking behaviors in rats based on biological sex and environmental light condition

Authors: *E. A. BREACH[1], A. VASQUEZ[2], R. AGARWAL[1], H. AJMAL[1], R. A. GONZALES[3], M. H. MONFILS[4], H. J. LEE[5];

[1]Col. of Natural Sci., [2]Dept. of Psychology, Univ. of Texas, Austin, TX; [3]Col. of Pharm., The Univ. of Texas at Austin, Austin, TX; [4]Dept. of Psychology, Univ. of Texas At Austin, Austin, TX; [5]Dept. of Psychology, Univ. of Texas at Austin, Austin, TX

Abstract: Current research aims to better understand the biological and environmental factors that contribute to alcohol use disorder(AUD). Intermittent access to alcohol in 2-bottle choice procedure (IA2BC) is a common model for alcohol consumption and binge-drinking behavior in a rat model of AUD. Research has shown that the majority of alcohol consumption during IA2BC occurs during the first 0.5-1.5 hours of the 24-hour access period; additionally, total alcohol consumption increases when the alcohol access period begins during the dark cycle rather than the light cycle. Even though females are generally known to drink more than males, no study has yet to compare how biological sex and environmental light conditions interact to affect binge-like alcohol consumption.Thus, this project examined alcohol consumption of male and female Long Evans rats under two different environmental light conditions(i.e., light and dark cycles). Rats were allowed to drink 15% (v/v in tap water) unsweetened alcohol under the IA2BC protocol (i.e., 24-hr access to alcohol on MWF) over the course of 5 weeks. The amount of alcohol consumed was measured in g per kg of body weight over the course of 30 min, 60 min, 90 min, 3 hr, and 24 hr intervals after the rats were presented with alcohol when the vivarium light came on (light cycle) or went off (dark cycle). After IA2BC, the rats that met threshold of sufficient alcohol consumption moved onto 2 weeks of Pavlovian conditioning (i.e., 20s light presentation with 10s sipper containing 15% alcohol) and 2 weeks of extinction (i.e., 20s light presentation with 10s empty sipper). Afterward, extinction memory testing was carried out along with spontaneous recovery testing two weeks laterResults showed no sex differences in alcohol consumption during the first 3 hrs of alcohol availability. However, at 24-hr time point, increased alcohol consumption was evident among females compared to males. We observed minimal binge-like drinking behavior, but rats in the dark cycle showed increased alcohol consumption at the 3-hr mark compared to the rats in the light cycle. No light or sex effect was found on conditioning or extinction as measured by sipper contacts. However, when testing for extinction recall and spontaneous recovery, an overall sex effect was observed. Females showed significantly greater response in alcohol seeking behavior ($p<0.05$); however, this effect was marginally modulated by the light condition ($p=0.09$) in which the sex difference was driven by females in the light cycle.Together, our study shows that biological sex and environmental factors play important roles in mediating drinking behavior.

Disclosures: E.A. Breach: None. **A. Vasquez:** None. **R. Agarwal:** None. **H. Ajmal:** None. **R.A. Gonzales:** None. **M.H. Monfils:** None. **H.J. Lee:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.10/OO12

Topic: G.03. Motivation

Support: NIH Grant DA044980
UROP 2023 Summer Individual Grant

Title: Early life stress produces sex-dependent differences in adult extinction learning in fear and motivational contexts

Authors: *M. J. MARTIN, C. A. BISHOP, J. B. TORRES, M. P. SADDORIS;
Univ. of Colorado Boulder, Boulder, CO

Abstract: A critical aspect of our understanding of mental health is understanding individual risk factors that may contribute to vulnerability to stress-related disorders such as PTSD or depression. One such factor is experienced during early development when the brain is rapidly developing. During this time, many people face adversity, with one CDC study indicating that approximately 2/3 of participants experienced at least one instance of severe stress during childhood. Furthermore, other studies have found that the risk of depression in females and drug abuse is positively correlated with the amount and severity of early life stress. Developmental stressors may also lead to disruption of appropriate behavioral responses to stress and reward in adulthood. Prior work from our lab using a brief wet bedding stressor around postnatal day 5 (P5) is sufficient to produce persistent fear in adults in a conditioned suppression paradigm along with fearful stimuli and motivated actions (Bercum et al. 2021; 2023). However, that prior study did not include both males and females nor did they separately compare the effects of reward versus fear extinction. Here, male and female pups were exposed to early life stress (ELS) from P2-P10 using a limited bedding approach (100g aspen shavings vs 300g controls), along with saturated wet bedding for 8h on P5. ELS rats were then returned to normal housing from P11 until wean. Meanwhile, control pups were left undisturbed until wean. As adults, all rats were trained to press a lever to obtain rewards up to VI60. Following a sequence of fear acquisition, extinction, and renewal in a novel set of contexts, rats were returned to the original reward context to again press for food. We then assessed suppression of pressing in the presence of the shock-paired cue versus a neutral cue for 3d, followed by 3d of instrumental extinction of the lever press. Males and females showed different vulnerability to the ELS stressor depending on the task features. During fear learning and extinction, female ELS rats showed elevated fear relative to female controls, but males in ELS and control groups were similar. In contrast, during the motivational components in conditioned suppression and reward extinction, male ELS rats were consistently different from male controls, while female ELS and controls were similar. Our data suggest that experiencing ELS may have distinct and sex-dependent impacts on adult vulnerability to stress and motivation disorders.

Disclosures: M.J. Martin: None. **C.A. Bishop:** None. **J.B. Torres:** None. **M.P. Saddoris:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.11/OO13

Topic: G.03. Motivation

Title: Male and female rats exposed to a socially-paired context decrease preference for a sucrose-paired context in a conditioned place preference paradigm

Authors: *A. A. LACKAN[1], K.-C. LEONG[2];
[1]Psychology, [2]Dept. of Psychology, Trinity Univ., San Antonio, TX

Abstract: According to the United States Centers for Disease Control and Prevention (CDC), 73.6% of adults aged 20 and over were overweight from 2017-2018, with 41.9% of these individuals also suffering from obesity; additionally, about 1 in 10 Americans have diabetes, and more than 1 in 3 Americans are prediabetic. A major contributing factor to these disease states is the maladaptive preference of sugar reward. Social interaction and social support have been found to diminish drug-seeking behavior, suggesting that social reward may combat the reward of substance abuse. We hypothesize that the rewarding effects of sugar may also be contested by social reward. In order to examine the competing nature of sugar and social reward, male and female rats underwent a conditioned place preference paradigm in which one context was paired with sucrose (5 pellets every 10 minutes) and the other context was paired with a conspecific. In brief, all rats were first given 2 days of sucrose priming, and then were conditioned for 30 minutes for 8 consecutive days, during which they alternated between contexts each day of conditioning, and sucrose and social reward were counterbalanced within groups. Results revealed that in the absence of any conspecific context, rats showed a significant preference for the sucrose-paired context, but rats who were conditioned with both a sucrose-paired and a conspecific context did not display any preference for the sucrose-paired context. The results of the present study suggest that social reward may diminish sucrose conditioned place preference, and further research will focus on elucidating the specific structures involved in this effect. The neuropeptide oxytocin (OXT) is known to be implicated in both social processes and reward. As such, we investigate the role of OXT in modulating this shift in preference between sucrose and social reward.

Disclosures: **A.A. Lackan:** None. **K. Leong:** None.

Poster

PSTR291. Sex Differences in Motivation and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.12/OO14

Topic: G.03. Motivation

Support: R01-AA029386
F31-AA030936

Title: Carbon dioxide reactivity predicts extinction memory to fear and alcohol cues in rats

Authors: *M. RASKIN[1], M. OLVERA[2], N. KELLER[1], L. A. AGEE[3], J. D. SHUMAKE[2], R. GONZALES[4], H. J. LEE[2], M. H. MONFILS[2];
[1]Inst. for Neurosci., [2]Dept. of Psychology, [3]Dept. of Neurosci., [4]Col. of Pharm., Univ. of Texas at Austin, Austin, TX

Abstract: Maladaptive associations underlie persistent responding to previously neutral stimuli. For example, cues present during a traumatic event may result in fear responses, and cues that precede rewards lead to seeking behavior (e.g., in addiction). These responses can be attenuated through extinction learning, where cues are repeatedly presented without the previously learned outcome—a core component of exposure therapy. Exposure therapy is effective for some patients, but not all. Another method to attenuate conditioned responses, retrieval-extinction, modifies the original associative memory via distinct neural mechanisms. We recently demonstrated that CO_2 reactivity predicts fear extinction memory and orexin activation, and that orexin activation predicts fear extinction memory, suggesting that a CO_2 challenge may enable identifying whether an individual is a good candidate for an extinction-based approach. We then extended this to show that CO_2 reactivity predicts appetitive extinction memory to food cues. The purpose of the present study was to determine whether the predictive power of CO_2 reactivity can be replicated in fear cues, generalizes to alcohol cues, and is specific to extinction for both fear and alcohol cues. In experiment 1, male rats were fear conditioned, received either extinction (n = 30) or retrieval-extinction (n = 28), and then underwent a long-term memory test. In experiment 2, male and female rats with a history of alcohol dependence underwent alcohol conditioning, received extinction (n = 35) or retrieval-extinction (n = 39), and then underwent a long-term memory test. All rats then received a CO_2 challenge, as outlined in Monfils et al. (2019), and we used the best subset approach to linear regression to determine whether CO_2 reactivity would predict extinction phenotype. CO_2 reactivity predicted fear extinction memory, explaining 42% of the variability in the total sample and 28% of the variability in the cross-validated (CV) holdout samples. In the retrieval-extinction group, CO_2 reactivity predicted fear extinction memory, explaining 19% of the variability in the total sample and 9% of the variability in the CV holdout samples. In experiment 2, CO_2 reactivity and sex predicted alcohol extinction memory, explaining 17% of the variability in the total sample and 7% of the variability in the CV holdout samples. In the retrieval-extinction group, no reliable predictors emerged from our analysis. We thus find that the predictive power of CO_2 reactivity is replicated for standard extinction and generalizes to retrieval-extinction for fear cues, and generalizes to alcohol cues for extinction, but not retrieval-extinction.

Disclosures: M. Raskin: None. **M. Olvera:** None. **N. Keller:** None. **L.A. Agee:** None. **J.D. Shumake:** None. **R. Gonzales:** None. **H.J. Lee:** None. **M.H. Monfils:** None.

Poster

PSTR292. Emotion: Investigations in Humans

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.01/OO15

Topic: G.04. Emotion

Support: NIH R01 MH124112

Title: Neural Decoding of 15 Affective States from Imagined Emotional Scenarios

Authors: *N. MUNCY[1], Y. DING[2], L. FAUL[3], K. S. LABAR[3];
[2]Ctr. for Cognitive Neuroscience, Duke Univ., [3]Duke Univ., [1]Duke Univ., Durham, NC

Abstract: The representation and organization of specific affective states in the brain, such as sadness, anxiety, and craving, remain elusive despite significant investigative efforts. Prior work in this area has typically involved univariate analyses, small sample sizes, simple stimuli, and small numbers of emotions, that limit sensitivity, generalizability, ecological validity, and impact on emotion theory. To better understand how affective states are reflected in brain activity patterns, we trained a multivariate pattern classifier to decode fMRI responses during an emotion induction task to identify relevant voxels (features) for an array of 15 affective states, and to determine which states share off-diagonal elements. We developed and validated a large set of two-sentence descriptions of hypothetical, real-world scenarios presented in a second-person perspective that span the affective states of interest. During fMRI scanning, 85 healthy adults (with ongoing recruitment) read and imagined each scenario in blocks of 5 exemplars per intended emotion, determined which emotion the scenarios best represented per block, and rated how intensely they experienced the corresponding affective state. Behavioral results were consistent with ratings data from the normative sample. Partial least squares discriminant analysis was conducted on whole-brain gray matter beta-estimates with a nested validation scheme to prevent overfitting (8-fold outer for independent cross validation, 5-fold inner for optimization of latent space). This approach achieved significant above-chance accuracy in decoding the 15 states (mean accuracy = 14.5%, chance = 6.67%; $p < .05$, 95% CI=[12.5%, 16.5%]) with moderate mean AUC = 0.62 (CI = [0.6, 0.64]), sensitivity = 0.61 (CI=[0.57, 0.64]), and specificity = 0.61 (CI=[0.56, 0.66]). Voxel importance maps revealed distributed cortico-limbic networks for each affective state that overlapped with univariate analyses, and inspection of off-diagonal elements suggested that conceptually-related brain states (e.g. fear and horror) generally agreed with participant's behavioral similarity ratings. These results implicate brain regions that are active for specific and related affective states, giving insight into the neural representation of a relatively large number of emotions, and provide additional evidence for the organization of these emotions in a semantic space.

Disclosures: N. Muncy: None. **Y. Ding:** None. **L. Faul:** None. **K.S. LaBar:** None.

Poster

PSTR292. Emotion: Investigations in Humans

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.02/OO16

Topic: G.04. Emotion

Support: NCNP Grant

Title: Increased brain activity associated with enhanced maternal affection for infants after childbirth

Authors: *K. HISHIKAWA, M. ABE;
Natl. Ctr. of Neurol. and Psychiatry (NCNP), Kodaira, Tokyo, Japan

Abstract: Background: Pregnancy and childbirth lead to a reorganization of brain circuitry, resulting in heightened affection for the baby and nurturing behavior in women. Animal studies observed active dopaminergic or oxytocinergic circuit of the brain that parallel higher parental behaviors. While it is challenging to express affection on an objective scale, this study defines the brain activity of the dopaminergic or oxytocinergic circuit in response to infants as the neural activity associated with affection towards infants. This study aims to investigate increased brain activity in response to infants after childbirth using functional MRI (fMRI).
Methods: We recruited 27 women who have experienced a first episode of childbirth in less than recent 3 months (postpartum group) and 30 age-matched women who have not experieced pregnant events (control group). Participants' liking for unfamiliar babies was assessed using a visual analog scale (Baby like VAS). Using fMRI, we measured brain activity while the pohotographs of baby faces were visually presented to the participants: both of the postpartum and control groups saw the babies or adults whom all of the participants had never seen before (i.e. other person's babies or other adult persons), The reason for using photographs of unfamiliar babies is to avoid the influence of personal attachment that comes with interacting with one's own baby during caregiving. Furthermore, in the postpartum group, the brain responses to their own babies were compared with those towards unfamiliar babies.
Results: The postpartum group showed higher Baby-like VAS scores to the other person's babies than the non-mother group (postpartum group: mean 74.1 ± 21.8 vs. control group: mean 86.7 ± 12.8, $p = 0.02$). The postpartum group showed greater activity in the right orbitofrontal cortex, right anterior insular cortex, right angular gyrus, and right precuneus than the non-mother group (cluster level of family-wise error $p= 0.05$ with a voxel level threshold uncorrected $p = 0.001$). Analysis of the regions of interest revealed stronger brain activity in the ventral tegmental area (VTA) in the postpartum group compared to the control group. Furthermore, in the postpartum group, a greater increase in brain activity was found in the right anterior insula and VTA when participants viewed photographs of their own babies compared to unfamiliar babies.
Conclusion: This study demonstrates increased brain activity in the VTA and right anterior insula among the postpartum women, suggesting that these brain regions undergo changes following childbirth and are involved in the augmentation of maternal affection towards infants.

Disclosures: K. Hishikawa: None. **M. Abe:** None.

Poster

PSTR292. Emotion: Investigations in Humans

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.03/OO17

Topic: G.04. Emotion

Support: National Science Foundation of China (31730038)

Title: Neural representation format in amygdala related to human memory for emotional faces

Authors: *T. LI, G. XUE;
Beijing Normal Univ., Beijing, China

Abstract: Human memory for emotional stimuli, such as emotional faces, are generally better than neutral stimuli, yet the neural representational mechanisms are not very well understood. In particular, although the amygdala has been consistently implicated in emotional face processing and memory, the information coding schema in this area and its contributions to episodic memory have not been systematically investigated. Here, we collected intracranial electroencephalography (IEEG) data from 14 epilepsy patients when they were encoding and recognizing negative, neutral and positive faces. We found clear behavioral evidence that patients have a higher d-prime rate when recognizing negative faces compared with neutral and positive faces. Using representation similarity analysis method, we further characterized the neural representations in the amygdala. We found stronger item-specific and category-specific representation for negative items than for neutral and positive faces in the amygdala, both of which were associated with subsequent memory. These results suggest the amygdala not only encodes emotional information, but also stimulus-specific information, and the stronger representations for negative faces could contribute to the better memory performances.

Disclosures: T. Li: None. **G. Xue:** None.

Poster

PSTR292. Emotion: Investigations in Humans

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.04/OO18

Topic: G.04. Emotion

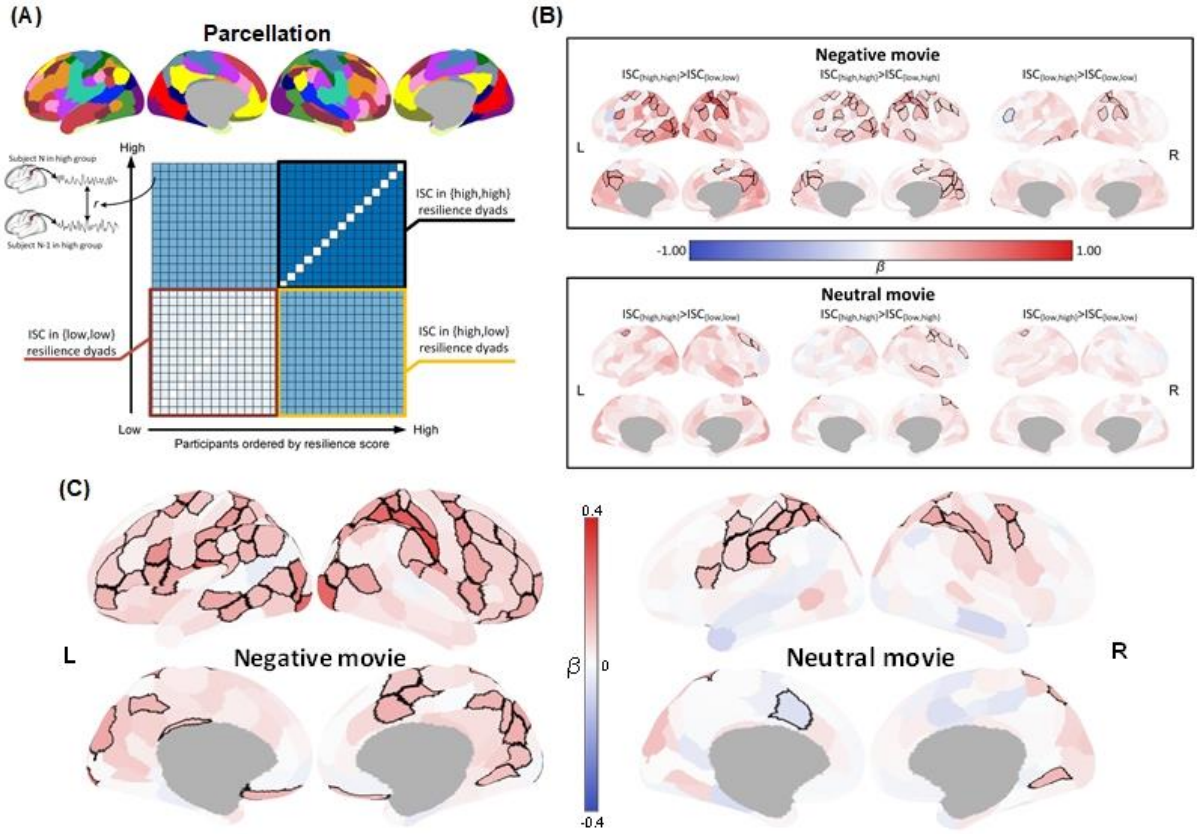
Support: Kavli Foundation

Title: Resilience-driven neural synchrony during naturalistic movie watching: an ultra-high field fMRI study

Authors: *S. YE[1], A. SALAMI[2], M. ZIAEI[1];
[1]Kavli Inst. for Systems Neurosci., Norwegian Univ. of Sci. and Technol., Trondheim, Norway;
[2]Umeå Univ., Umea, Sweden

Abstract: Resilience, regarded as a capacity to effectively cope with adversities, could protect individuals against psychological distress induced by negative emotions. The way people perceive emotional cues is thus influenced by their level of resilience. It is still unclear, however, how the neural correlates of resilience can be measured in daily life. In this study, we examined

how resilience level is related to brain patterns across individuals. We presented two movies, one with negative and one with neutral emotional valence to 62 healthy younger (Mean age of 25.68 ± 4.30 years, 29 females) participants while in the 7T MRI scanner. We combined inter-subject correlation (ISC) with inter-subject representational similarity analysis (IS-RSA) to investigate the association between resilience level and brain-to-brain synchrony while watching movies. We further explore the modulation effect of intolerance of uncertainty (IU), a personality trait that may shape biased perception, on the association between resilience and brain synchrony. Results indicated resilience-driven brain synchrony of a wider set of brain regions in the negative movie (the prefrontal area, temporal lobe, and dorsal attentional network [DAN]) than in the neutral movie (mainly located in the DAN). The high-resilience individuals had similar neural activities to their peers whereas low-resilience individuals show more variable neural activities. Moreover, increased IU enhanced resilience-driven synchrony in the default mode network and dampened resilience-driven synchrony in the DAN. These results suggested that neural response to emotional stimuli is similar in high-resilience individuals but is idiosyncratic in low-resilience individuals, and such resilience-driven neural similarity is modulated by intolerance of uncertainty.



Disclosures: **S. Ye:** None. **A. Salami:** None. **M. Ziaei:** None.

Poster

PSTR292. Emotion: Investigations in Humans

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.05/OO19

Topic: G.04. Emotion

Support: NSERC CGS-M Scholarship

Title: The impact of emotional stimuli on arousal and task performance.

Authors: *B. WU[1], E. STEWART[1], B. BUTLER[2], D. MITCHELL[1];
[2]Physiol. & Pharmacol., [1]Univ. of Western Ontario, London, ON, Canada

Abstract: In times of emotional arousal, it is hypothesized that neural processes are triggered to "heighten" our senses to better respond to threatening stimuli. Some studies have tested this by exposing participants to emotional sounds to determine their impacts on visual acuity. However, the results have been mixed, sometimes showing improvements in vision, but other times showing detrimental effects or no effects at all. Previous studies have not investigated interactions between arousal induced by emotional sounds and visual acuity. Here, we aim to evaluate how emotional sounds influence arousal and performance in an orientation detection task. Participants viewed Gabor patches (sinusoidal luminance gratings) on the right or left side of fixation and indicated whether the Gabor patches were tilted left or right. To account for individual differences in baseline visual acuity, an orientation detection threshold task at the beginning of the experiment was conducted to select the orientation associated with 70% accuracy. The presentation of Gabor patches was presented concurrently with auditory stimuli selected from the International Affective Digital Sounds Database that varied in valence (negative or neutral). A no sound control condition was also included. Visual performance was measured by the proportion of correct responses for each condition as well as reaction time. Arousal was measured by tracking pupil dilation throughout the experiment using the EyeLink 1000 eye tracker. Preliminary results from (14, 36 more to be collected) participants showed significantly greater accuracy (5.72 percent difference ± 0.10 SE) and significantly faster reaction times (22 ms difference ± 0.45 SE) in the negative condition than the neutral condition and significantly greater accuracy (5.71 percent difference ± 0.1 SE) and faster reaction times (55 ms difference ± 0.24 SE) in the negative condition than the no sound condition. Additionally, pupil dilation from baseline during the presentation of the Gabor patches was significantly greater (0.02 mm difference ± 4.0×10^{-4} SE) in the negative condition compared to the neutral condition and significantly greater (0.20 mm difference ± 5.0×10^{-4} SE) in the negative condition compared to the no sound condition. Our findings provide evidence that negative sounds significantly increase visual acuity and arousal. These findings will delineate how changes in arousal due to environmental factors can alter sensory processing, leading to changes in human performance. In addition, they will pave the way for further work examining the neural mechanisms behind sensory enhancement in emotionally arousing contexts.

Disclosures: B. Wu: None. **E. Stewart:** None. **B. Butler:** None. **D. Mitchell:** None.

Poster

PSTR292. Emotion: Investigations in Humans

Location: WCC Halls A-C

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Program #/Poster #: PSTR292.06/OO20

Topic: G.04. Emotion

Support: 5U01NS117839-03 [JAT, SGO, DRK]

Title: Single-neuron amygdala activity during emotion recognition

Authors: *J. V. MACHNIK[1], R. N. TIEN[1], M. L. DARWIN[1], L. BASHFORD[3,1], S. G. OJEMANN[1], J. A. THOMPSON[1,2], D. R. KRAMER[1];
[1]Dept. of Neurosurg., [2]Dept. of Neurol., Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [3]Biosci. Inst., Newcastle Univ., London, United Kingdom

Abstract: The amygdala is known to process biologically relevant, emotionally valenced stimuli. Neuroimaging studies in humans have demonstrated that the amygdala responds to a wide range of stimuli, however fMRI is not well suited to characterize the precise neural response profiles. The required spatial and temporal resolution can be obtained from intracranial electroencephalography (iEEG). Previous iEEG research has identified both early and later responses in the amygdala during a range of face presentation stimuli, suggesting the amygdala plays an important role in the rapid evaluation of emotion. However, it remains to be elucidated how the time course of the response relates to the complexity of various emotions. Here we use iEEG with micro-contact depth electrodes to evaluate single neurons in the amygdala of human patients undergoing monitoring for seizure localization (N=6, M_{age}=39.6 years, SD_{age} =10.7, 1 male). A set of seven emotions (six basic and neutral) from a standardized set were presented to study participants for 2 seconds followed by a response period in which patients selected the emotion they saw. We divided the basic emotions into two categories for analysis: lower order emotions (happy, sad, and angry) and higher order emotions (disgusted, fearful, and surprised). Behavioral results demonstrated that within 250 ms of image onset, amygdala neurons significantly responded to sad, angry, neutral, fearful, and surprised emotions. Further investigations revealed the quickest responses overall were for the lower order emotions than the higher order ones. Furthermore, we found a significant misclassification of the higher order emotions (e.g., fear and surprise) and neutral, compared to the lower order emotions (e.g., happiness, sadness, and anger). Here we present initial evidence that the neural response in the amygdala is related to the complexity of the emotion being processed. Higher order emotions have more complex activation patterns which occur later than lower order emotions, suggesting a top-down processing role in emotion requiring a more nuanced understanding of emotional context. Further work should seek to simultaneously record from both cortical and deep areas to further understand emotional processing in the brain.

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Poster

PSTR292. Emotion: Investigations in Humans

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Program #/Poster #: PSTR292.07/OO21

Topic: G.04. Emotion

Support: NIMH R01 MH116026

Title: Temporal dynamics of negative emotion and reappraisal in the amygdala

Authors: *K. BO[1], P. J. GIANAROS[3], T. D. WAGER[2];
[2]Dept. of Psychological and Brain Sci., [1]Dartmouth Col., Hanover, NH; [3]Univ. Pittsburgh, Univ. Pittsburgh, Pittsburgh, PA

Abstract: Reappraisal is an emotion regulation strategy that involves reinterpreting meaning and context to alter emotional experience. It is widely accepted that reappraisal can successfully down-regulate amygdala activation, a mechanism central to the affective generation process. However, some recent studies and meta-analyses have not confirmed this effect. To gain deeper insight, the current study further delves into the temporal dynamics of the amygdala's Blood-Oxygen-Level-Dependent (BOLD) time series in two large community samples (n=182 and n=178) who viewed and reappraised aversive and neutral images from the International Affective Picture System (IAPS) during fMRI scanning. Employing a smooth Finite Impulse Response (FIR) model, we estimated the amygdala's hemodynamic response during the cue, stimulus, and rating periods. Our findings reveal that both viewing (‘Look Negative’) and reappraising (‘Reappraise’) negative pictures evoked significant hemodynamic responses across laterobasal (LB), centromedial (CM), and superficial (SF) amygdala subregions. Responses occurred relatively late relative to picture onset, likely reflecting an extended image appraisal and comprehension process, and different subregions showed differences in the shape and latency of hemodynamic responses: BL and SF amygdala exhibited an earlier peak, at 10s post-stimulus onset, while CM peaked later, at 16s. However, evoked responses during Reappraise and Look Negative trials were equivalent. We also observed a habituation effect across trials during passive viewing (‘Look Negative’) that was absent in 'Reappraisal' trials, resulting in a significant condition x time interaction. These findings suggest that reappraisal does not significantly reduce amygdala responses to aversive pictures in this sample, and may interfere with habituation processes that are operative during passive viewing conditions.

Disclosures: K. Bo: None. **P.J. Gianaros:** None. **T.D. Wager:** None.

Poster

PSTR292. Emotion: Investigations in Humans

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Program #/Poster #: PSTR292.08/OO22

Topic: G.04. Emotion

Support: NIMH grant R01MH126531
Gift funds from Einhorn Collaborative

Title: Mechanistic investigation of dyadic emotional connection: the emotional connection screen

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Abstract: Human social connectedness is a complex phenomenon that stems in the early-life relationships with parents/caregivers. In pediatrics, promoting healthy early relationships, or the ability to form and maintain stable and nurturing parent/caregiver-child relationships, has been made a priority officialised in 2021 by a paradigm shifting statement of the American Academy of Pediatrics. Despite the importance of early parent-child relationships to child health, development and wellbeing, advances in systematic measurement of the quality of parent/caregiver-child dyadic interactions that can readily be used in clinical or research settings are scarce. With this in mind, the Nurture Science Program at Columbia University has developed an emotional connection screen; an observer-based assessment of dyadic interaction behaviors that translate emotional transfer between mother and infant. Here, we further investigate the mechanistic underpinnings of dyadic emotional connection using video-based data obtained from the 4-month relational health assessment as part of the COMBO Initiative. In a remote video visit, mothers were asked to interact face-to-face with their infant for 2 minutes, without using toys or pacifiers. A subset of 46 2-min videos was macro-coded with the emotional connection screen for a gestalt assessment of the dyad's global emotional connection (scores ranging from 0 to 100). The subset was also micro-coded using Boris, an open-source event-logging software, to gather timed-sequential data with millisecond precision on an array of maternal and infant interaction behaviors like gaze, touch (i.e., static, affectionate, caregiving, playful, attention seeking), reaching, leaning in, back arching, etc.The subset of 46 videos was composed of 32.21 (5.19) year old mothers and their 5.51 (2.33) month old infant, and 60% (n=28) of the infants were males. The mean score on the emotional connection screen was 50.48 (24.92), which represents 48% (n=22) of the dyads scoring high on emotional connection, 24% (n=11) scoring low on emotional connection, and the rest (n=13, 35%) with variable levels of emotional connection throughout the 2-min face-to-face interaction. At the micro-analysis level, preliminary results show a high correlation (r=0.82) between mother-infant mutual eye gaze and overall emotional connection scores. The contribution and patterning of microcoded maternal and infant interaction behaviors will be further investigated using sequential patterning mining techniques to identify the fundamental sequential patterns of multimodal behaviors during moments of high and low emotional connection.

Disclosures: **A. Lavallee:** None. **Q.J. Manning:** None. **M.A. Reimers:** None. **M. Moore:** None. **M. Kyle:** None. **M. Hussain:** None. **R. Xu:** None. **M. McKiernan:** None. **E. Arduin:** None. **M. Kuromaru:** None. **E. Greeman:** None. **D. Dumitriu:** None.

Poster

PSTR292. Emotion: Investigations in Humans

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Topic: G.04. Emotion

Support: CONACYT 1139115

Title: Description of the dimensions of burnout syndrome in medical students of the Universidad Veracruzana (2021-2023)

Authors: *S. SOSA ALVARADO[1,2], F. D. VÁZQUEZ-MARTÍNEZ[3], M. ACOSTA-FERNÁNDEZ[5], N. MATZUMOTO-BENÍTEZ[4], R. RAMOS-CASTRO[4], E. PEREDO-RIVERA[6];
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Abstract: Burnout syndrome is an occupational phenomenon resulting from chronic work stress that has not been successfully managed. This syndrome has been identified in different professions, however it is more frequent and has greater repercussions in specialist doctors, presenting a prevalence range from 30 to 69% in general practitioners and specialists. Burnout syndrome is characterized by a lack of enthusiasm, a gradual loss of energy and general exhaustion, the presence of feelings of insensitivity and cynicism, and a tendency for the person to negatively evaluate their self-perception and job performance. A cross-sectional and descriptive study was carried out in last-year medical students who were doing their social service, from a public university in the state of Veracruz, Mexico; to evaluate the dimensions of the burnout syndrome by applying the Maslach Burnout Inventory. A convenience sampling was carried out, with a total of 218 participants. The results obtained show that the majority of the students 53.21% have a high degree of ocupational exhaustion, contrary to depersonalization where the majority 49.54% have a low degree. Regarding personal fulfillment, the majority 52.29% have high scores (more than 40 points) in this dimension. In addition to this, a multivariate analysis was applied with a cluster type grouping technique. Defining 5 Groups, characterizing Group 1 for presenting low scores of ocupational exhaustion and depersonalization, contrary to Group 5 who present high scores in these dimensions. These results are similar to those found by Álvarez et al. in 2019, where through a systematic review of the prevalence of burnout syndrome in Latin American doctors between 2012 and 2018, they identified that the majority present high levels of emotional exhaustion.

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Poster

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Program #/Poster #: PSTR292.10/OO23

Topic: G.04. Emotion

Title: Activity changes of the subthalamic region during emotional processing revealed by LFP data acquired from the Closed-loop DBS system

Authors: *T. MATSUHASHI[1], N. TANI[1], T. EMURA[1], Y. KIMOTO[1], K. HOSOMI[1], R. FUKUMA[2], S. OSHINO[1], T. YANAGISAWA[2], H. KISHIMA[1];
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Abstract: Introduction: The human subthalamic nucleus (STN) region is involved in the processing or transmission of emotional information. Recently, the DBS device equipped with a closed-loop system that measures and records local field potential (LFP) from electrodes implanted in the basal ganglia region and provides feedback on stimulus intensity in response to changes in LFP has been introduced into clinical practice. In the study of psychology, by collecting and analyzing emotionally stimulating data, such as videos that elicit various emotions, and human emotional response data to the stimuli, it has been shown that models using many emotion categories (high-dimensional emotion models) can explain human emotional responses better than conventional models based on a few basic emotions (AS Cowen et al., 2017). In this study, by using the Closed-loop DBS system, we attempted to obtain LFP changes in response to video stimuli with the labeling of emotional categories in a preceding psychological study.Methods: This study was performed on Parkinson's disease patients(n=18) who underwent implantation of the Closed-loop DBS system at our hospital. LFPs were recorded while watching a series of videos categorized into specific emotional categories. The participants were asked to select the emotional category corresponding to the videos and score on the degree of their emotion. Emotion labeling scores were normalized for each participant and treated as scoring intensity. We performed the frequency analysis of the LFP, and calculated the rate of change from the baseline at rest, in each band power in the delta, theta, alpha, beta, and gamma bands. Multiple regression analysis was performed between the band power change rates, and the emotion labeling scores intensity for each video category.Results: In viewing the category of videos that arouse appetite, the beta band power of the left STN was negatively correlated with the scoring intensity($p<0.05$), whereas the gamma band power of this location was positively correlated with the scoring intensity($p<0.05$). In viewing the category of videos that elicit fear, the Delta band power of the right dorsal STN was negatively correlated with the scoring intensity($p<0.05$), and the theta band power of this location was positively correlated with the scoring intensity($p=0.07$).Conclusion: Power changes in the frequency band of STN LFP may be informative as an indicator of the degree of emotional response to stimuli of Parkinson's patients

Disclosures: **T. Matsuhashi:** None. **N. Tani:** None. **T. Emura:** None. **Y. Kimoto:** None. **K. Hosomi:** None. **R. Fukuma:** None. **S. Oshino:** None. **T. Yanagisawa:** None. **H. Kishima:** None.

Poster

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Topic: G.04. Emotion

Support: President of the University of Toyama in 2021–2022

Title: Investigation of responsible molecules to control subjective well-being in humans

Authors: *Y. INADA[1], C. TOHDA[2];
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Abstract: Subjective well-being (SWB) is an important research topic being addressed from a variety of perspectives, including psychology, public health, and medicine. The fact that SWB is influenced by physical activity and cognitive activity, and vice versa SWB affects physical activity and cognitive activity, suggesting that the locomotor system and cognitive function closely relate to mental health. However, the molecular basis of these interactions has not been clarified at all. This clinical study aimed to investigate what are relating activities to SWB, and find molecules from the blood circulation, which are responsible for controlling SWB. Subjects were healthy elderly people aged 65 and over. Evaluation items were Happiness and Quality of Life as SWB scale, cognitive function (CF), motor function (MF) and daily physical activity (DPA). Based on all scores in those items, Structural Equation Modeling was conducted. The most fit model showed that CF, MF and DPA are sequentially needed to explain SWB. Next, to elucidate features of elder people with high SWB, subjects were divided by their SWB scores and other activities patterns. As a results, scoring patterns were divided into 4 groups. High SWB was associated with high scores in CF, MF and DPA. Plasma samples of typical subjects in those 4 groups were served for tandem mass tag-based quantitative proteomics. Comprehensive analysis indicated that the level of protein X was different depending on SWB level. Furthermore, the protein X level was significantly correlated with DPA, such as calorie consumption and moderate to vigorous physical activity. More analyses are ongoing. No molecular explanation has not been achieved why physical activity, cognitive activity, and social activity affect SWB. The present study has the potential to answer the question and to provide a new perspective for mental health.

Disclosures: Y. Inada: None. **C. Tohda:** None.

Poster

PSTR292. Emotion: Investigations in Humans

Location: WCC Halls A-C

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Program #/Poster #: PSTR292.12/OO24

Topic: G.04. Emotion

Title: Altered autonomic balance by mood-congruent music in heart-broken people: an fMRI study

Authors: *L.-Y. CHIEN, W.-J. KUO;
Yang Ming Chaio Tung Univ., Taipei, Taiwan

Abstract: People can change their mood through music, which has been applied to individuals with certain clinical cases, such as Major Depressive Disorder (MDD). To investigate the neural relevance of mood changes induced by music, we organized pieces of music into two contexts based on the congruence between the music's valence (pleasant vs. unpleasant) and the listeners' mood state. In the congruent condition, there were five songs presented, starting with two sad songs and transitioning to three happy ones. In the other condition, all five songs were happy. The participants were females who had recently gone through a romantic relationship break-up. Resting fMRI sessions were conducted before and after the music sessions of the two conditions, on separate days. To evoke feelings of hurt and sadness, participants were shown a photo of their ex-partner during the resting fMRI sessions. Electrocardiogram (ECG) data was recorded while participants listened to the music, and based on this signal, we observed higher heart rate variability (HRV) in the congruent condition. Conversely, functional connectivity (rsFC) between the right anterior insula (rAIC) and anterior cingulate cortex (ACC) decreased after listening to music in the congruent condition. Overall, our findings demonstrate that mood-congruent music in the beginning, as indicated by higher HRV, may gradually promote a better balance between the parasympathetic and sympathetic systems, thus potentially disrupting the connectivity of the rAIC-ACC network (i.e., the salience network).

Disclosures: L. Chien: None. **W. Kuo:** None.

Poster

PSTR292. Emotion: Investigations in Humans

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Program #/Poster #: PSTR292.13/OO25

Topic: G.04. Emotion

Title: Math Anxiety and its relationship with Arithmetic processing and Becks anxiety

Authors: *S. ZAMORA LUGO[1], T. CIBRIAN-LLANDERAL[2];
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Abstract: Introduction: Among the most mentioned mathematical cognitive processing skills in the literature are abstract thinking and visuospatial processing. It has been suggested that

intellectual aspects such as poor abstract thinking or poor visuospatial processing may contribute to the development of Math Anxiety (In this regard, one study showed that people with high MA reported a worse sense of direction and obtained poorer performance on small- and large-scale behavioral tests of spatial abilities. Methodology: An observational, retrospective, descriptive and cross-sectional study was carried out. A questionnaire on the Prevalence of Mathematical Anxiety in university students was applied digitally through the Google Forms platform. 63 university students were evaluated according to the inclusion criteria to be part of the final sample, who had an average age of 23.38 (SD ± 5.5), 33.3% were male and 66.7% female. The instruments used were the Mathematical Anxiety Index, the Beck Anxiety Inventory) and a task of arithmetic processing. Results: The average Beck Anxiety Inventory score was 21.7 (SD ± 11.8). 11.1% obtained a Low rating, 44.4% Mild, 28.9% Moderate and 15.6% Severe. The average response time was 4.6 seconds (SD ± 1.8) and the average hit was 70.8 (SD ± 7.7). A correlation analysis was made between the IAM with the average Hits, Additions Hits, Subtraction Hits, Simple Operations Hits and Complex Operations Hits. Significant correlations were observed with the variables Hit (rho = -0.3, p = 0.02), HitS (rho = -0.4, p = 0.001) and HitCom (rho = -0.3, p = 0.01). A correlation analysis was also carried out between the AMI with the average Response Time (RT)0, RT of additions, RT of Subtractions, RT of Simple operations, and RT of Complex operations. Significant correlations were observed with the variables RT (rho = 0.42, p < 0.001), TRS (rho = 0.5, p < 0.001) and RT Com Complex (rho = 0.52, p < 0.001). Conclusion: It was observed that, in the simple additions, the participants required less time to generate the correct answer, which is related to the automatic recovery of the arithmetic facts, while in the complex subtractions the opposite happened. The observed response times coincided with what was reported, in that more difficult operations require more time to generate a response, for example, the participant will answer an addition faster than a subtraction or an operation with a digit compared to one. operation of more than one digit, this because it requires more time to make use of the work memory in operations with greater difficulty.

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Poster

PSTR292. Emotion: Investigations in Humans

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Program #/Poster #: PSTR292.14/PP1

Topic: G.04. Emotion

Title: Same emotion different stimuli: creating a contextually rich MRI paradigm for studying nostalgia

Authors: *H. S. DOSHI[1], C. KORNBREK[2], A. K. ANDERSON[1], M. GONZALEZ[1]; [1]Psychology, [2]Biomed. Engin., Cornell Univ., Ithaca, NY

Abstract: Advances in affective science show that emotions, especially those culturally and socially embedded, are deeply contextual. For example, though nostalgia is possibly a universal human emotion, what evokes nostalgia is rooted in one's individual experiences. However, neuroimaging paradigms usually involve the use of "universal" stimuli to evoke putative universal cognitive and affective phenomena. In this study, we developed a system for creating context-specific standardized stimuli that can be used in MRI paradigms to measure nomothetic phenomena (nostalgia) in an idiographic manner (culturally specific). We web-scraped 229 realistic images of foods commonly consumed in India (134) and the USA (95). Foods ranged from appetizers to festival meals, represented all macroregions within the nation, and were uniformly distributed across a low-high calorie range. Raw foods, sweet items, drinks, brands, and aesthetic images were excluded to create a collection of regular meals commonly found at home while controlling for glucose. In consideration of fMRI factors, images were standardized for size, color scale, pixels, grayscale, and hue. Saturation and texture could not be normalized so were measured to adjust our statistical models. 46 participants who currently live in the US, but grew up in either the US or India, rated each image on a 7-point Likert for familiarity, comfort, and nostalgia twice, with a gap of at least a month. Participants were significantly hungrier after completion of the paradigm ($t = 4.29$, $p = 0.00$), which replicated the second time ($t = 3.06$, $p < 0.01$). There were group differences in individual measures of nostalgia such that individuals tended to find developmentally consistent foods more nostalgic ($F(1,9068) = 1119.56$, $p = 0.00$). On an individual level, most developmentally consistent foods were highly familiar but differences in ratings of comfort and nostalgia emerged. That is, all participants demonstrated evidence of experience of nostalgia for different foods. Participants found an average of 46 food items, majority of which were culturally consistent, of the total set to be highly nostalgic (> 5). Test-retest reliability for familiarity, comfort, and nostalgia was $r = .762$, .764, and .780 ($p < 0.01$) respectively. Further testing for cross-validation with a new sample is underway. 27 items were removed overall, and ten new items were added to Indian foods to create a final set of 202 standardized, natural food images. This preliminary evidence suggests that our protocol can be used to create a culturally sensitive, but standardized image set, which can later be used in the MRI to elicit a universal experience.

Disclosures: **H.S. Doshi:** None. **C. Kornbrek:** None. **A.K. Anderson:** None. **M. Gonzalez:** None.

Poster

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Topic: G.04. Emotion

Support: NIH R01 MH124112

Title: Neural decoding of 15 affective states from emotional movies

Authors: *Y. DING[1], N. MUNCY[2], L. FAUL[2], K. S. LABAR[2];
[2]Duke Univ., [1]Duke Univ., Durham, NC

Abstract: In this study, we investigatedthe relationship between discrete emotional states and patterns of brainactivity by experimentally inducing 15 emotions (amusement, anger, anxiety,awe, calmness, craving, disgust, excitement, fear, horror, joy, neutral,romance, sadness, and surprise) in participants during fMRI scanning.Previously-validated brief video clips (3-12 s long) were used for the emotioninduction and were presented in blocks of 5 clips per intended emotioncategory. One hundred and six healthy adult participants (73 female, mean age =30.8 (8.44)) were recruited from the local community. Analysis of participantin-scanner affective responses from 54 completers indicate successful emotioninduction, with a mean concordance of 73% ($p < 0.05$, CI [71%, 75.5%])between the participants' endorsement and the emotion labels assigned to thestimuli based on the normative ratings. We used a whole-brain general linearmodel to identify the block-level grey-matter beta-weights for subsequentlyclassifying the 15 emotional states with a partial least squares discriminantanalysis (PLS-DA). A nested cross-validation scheme (an 8-fold outer loop forsubject independent cross validation and a 5-fold inner loop for identifying anoptimal number of latent variables for classifying each emotion) was used whentraining the PLS-DA classifiers to improve their generalizability. The PLS-DAclassifiers achieved a significant above-chance level mean accuracy across the15 emotions (mean = 34.8%, $p < 0.05$, 95% CI [32.4% 37.2%]), wherechance-level accuracy is 6.67%. The area under the curve (AUC) (mean = 0.82, 95% CI [0.79 0.85]), sensitivity (mean = 0.76, 95 % CI [0.73 0.80]), andspecificity (mean = 0.74, 95 % CI [0.69 0.78]) also indicate good decodingperformance. The pattern classification results revealed unique, distributedpatterns of cortico-limbic activity for each of the 15 emotions, indicating ameaningful relationship between brain activity patterns and theexperimentally-induced emotional states. These robust findings indicate that itis possible to decode the specific emotional states that someone might besubjectively experiencing based on brain activation patterns alone across avariety of emotions.

Disclosures: Y. Ding: None. **N. Muncy:** None. **L. Faul:** None. **K.S. LaBar:** None.

Poster

PSTR293. Emotion: Investigations in Non-Human Vertebrates

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Title: Time-invariant prefrontal activity patterns during repeated exposure to intense threat

Authors: *O. SYLTE, H. MUYSERS, H.-L. CHEN, M. BARTOS, J.-F. SAUER;
Albert Ludwig Univ. of Freiburg, Freiburg im Breisgau, Germany

Abstract: Intense threat elicits action in the form of active and passive coping. The medial prefrontal cortex (mPFC) executes top-level control over the selection of threat coping strategies, but the dynamics of mPFC activity upon continuing threat encounters remain unexplored. Here, we used 1-photon calcium imaging in mice to probe the activity of prefrontal pyramidal cells during repeated exposure to intense threat in a tail suspension (TS) paradigm. A subset of prefrontal neurons displayed selective activation during TS, which was stably maintained over days. During threat, neurons showed specific tuning to active or passive coping. These responses were unrelated to general motion tuning and persisted over days. Moreover, the neural manifold traversed by low-dimensional population activity remained stable over subsequent days of TS exposure and was preserved across individuals. These data thus reveal a specific, temporally and inter-individually conserved repertoire of prefrontal tuning to behavioral responses under threat.

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Poster

PSTR293. Emotion: Investigations in Non-Human Vertebrates

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Program #/Poster #: PSTR293.02/PP4

Topic: G.04. Emotion

Title: Lateral hypothalamus-dorsal raphe circuitry: anatomy and function in emotional behaviors

Authors: *R. SADRETDINOVA, Z. BENMAMMAR, C. D. PROULX;
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Abstract: The dorsal raphe nucleus (DRN) regulates affective behaviors and energy balance. Emotional states might be encoded in DRN by neural inputs from numerous brain regions. Although one of the major reciprocal synaptic partners of DRN is the lateral hypothalamic area (LHA), the circuitry between LHA and DRN was not characterized yet. In the current study, we use anterograde and retrograde viral strategies to investigate the anatomical and functional reciprocal circuitry between the LHA and the DRN. Specifically, we targeted DRN cells receiving input from LHA (DRN input) and DRN cells projecting on LHA (DRN output) to express either fluorescent proteins or genetically-encoded calcium indicators. Our results show that DRN input and DRN output neurons are largely two distinct neuronal populations that have differential spatial distribution. LHA makes synaptic contact with 5-HT and non-5-HT neurons in the DRN, which is spatially biased to the ventromedial part and dorsolateral parts of the DRN, respectively. DRN output neurons appeared to be mostly non-serotonergic indicating the bias of the retroAAV-FlpO used. Both DRN input and DRN output neurons target a stereotypical set of subcortical regions while there were no terminals detected in cortical areas. Neural activity of

studied populations was increased in aversive stressful contexts such as air puff and tail suspension. Overall, these results show that 1) anterograde transsynaptic tracing can be applied to identify DRN neurons innervated by the LHA, 2) LHA targets specific DRN neuron populations with a spatial bias, 3) DRN input neurons projects mostly to subcortical limbic regions, 4) DRN input and DRN output neurons are involved in encoding aversive signals.

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Poster

PSTR293. Emotion: Investigations in Non-Human Vertebrates

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Topic: G.04. Emotion

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Title: Exploring brain-wide neural dynamics underlying psilocybin's psychoactive effects in zebrafish

Authors: *A. M. ROSENBERG[1], D. BRAUN[1,2], R. HARUVI[1], D. MALAMUD[1], R. BARBARA[1], T. KAWASHIMA[1];
[1]Weizmann Inst. of Sci., Rehovot, Israel; [2]The Jerusalem Mental Hlth. Ctr., Jerusalem, Israel

Abstract: Serotonergic psychedelics are emerging therapeutics for psychiatric disorders, yet their underlying mechanisms of action in the brain remain largely elusive. Zebrafish have evolutionarily conserved serotonergic circuits, including subcortical targets such as the brainstem regions and the cerebellum, making it a promising model for studying subcortical actions of serotonergic drugs. Here, we investigated the effects of psilocybin, a psychedelic serotonin receptor agonist, on larval zebrafish behavior and brain-wide neural dynamics. Using machine learning analyses of precise body kinematics, we identified two main behavioral effects of acute psilocybin treatment on free swimming behaviors: [i] increased rapid scooting in the absence of visual stimuli (stimulatory effect) and [ii] preventing changes in swim patterns after stress exposure (anxiolytic effect). We further explored the underlying neural mechanisms using c-*fos* mapping and whole-brain neural activity imaging. We identified several brain regions which respond to psilocybin treatment. These findings provide direct insights into how serotonergic psychedelics impact subcortical networks to affect animal behaviors.

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Poster

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Topic: G.04. Emotion

Support: 2021ZD0202804
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Title: A competitive inhibitory circuit for selection of unpredictable threat response and anxiety induction

Authors: *S.-W. TENG[1,2], Z.-Y. CHEN[2];
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Abstract: Anxiety is elicited by the excessive apprehension about possible unpredictable threats. Previous studies have identified the role of the bed nucleus of the stria terminalis (BNST) in regulating unpredictable threats and anxiety. However, the specific circuit links unpredictable threats to anxiety is still unclear. Here, we used Vgat-Cre mice combined with in vivo fiberphotometry and optogenetics technology to identify the selective vBNST circuit responsible for the defensive responses to unpredictable threat signal and anxiety. We found that vBNST Vgat neurons showed selective activation to unpredictable threat signals, which was necessary for the freezing behavior to unpredictable threats. Next, using activity-dependent neuronal circuit tracing combined with optogenetics technology, we found that insular cortex (IC) provides the excitatory inputs to vBNST, and the vBNST Vgat neurons which received the forward inhibition signal from the lateral nucleus of the amygdala (CeL) somatostatin (SOM) neurons showed selective activation in response to unpredictable rather than predictable threats. In addition, we further found that artificially activation of the circuits from vBNST unpredictable CS (CS-) activated cells to the median nucleus of the amygdala (CeM) or the ventral lateral periaqueductal grey (vlPAG) could elicit anxiety-like or freezing behaviors respectively, which suggest that the vBNST Vgat neurons are responsible for unpredictable threat signals induced anxiety-like and freezing behavior. Finally, we found that vBNST CS- responsible neurons showed increased activities to multi-unpredictable threat signals and inhibiting vBNSTVGAT-CeM circuits could rescue anxiety-like behavior in chronic unpredictable mild stimulation(CUMS) models. Our findings identify the specific neural circuits of vBNST Vgat neurons responsible for unpredictable threats and provide the neural circuitry basis for unpredictable threats induced anxiety behavior, which provide potential value in anxiety therapy.

Disclosures: S. Teng: None. **Z. Chen:** None.

Poster

PSTR293. Emotion: Investigations in Non-Human Vertebrates

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Program #/Poster #: PSTR293.05/PP7

Topic: G.04. Emotion

Support: Medical Research Council (MRC-MR/V033492/1) of the United Kingdom

Title: Two faces of anxiety: the differential efficacy of acute SSRI and ketamine to ameliorate anxiety-like behaviour in the marmoset induced either by ventromedial prefrontal overactivation or orbitofrontal inactivation

Authors: *K. G. MULVIHILL, L. MCIVER, A. C. ROBERTS;
Physiology, Develop. and Neurosci., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Extensive individual variability in pharmacological treatment efficacy remains a persistent obstacle in ameliorating clinical anxiety. The most common first-line treatments are selective serotonin reuptake inhibitors (SSRIs), but these typically show anxiolytic action only following weeks of treatment; hence the growing interest in rapidly-acting agents like ketamine. However, there is also evidence in humans for short term actions of SSRIs to reduce aversive processing, although again there is marked variation in the response (Bhagwagar et al., 2004; Di Simplicio et al., 2014). Indeed, anxiolytic efficacy of acute SSRIs has been shown to be genotype dependent in marmoset monkeys (*Callithrix jacchus)* (Santangelo et al., 2016). We propose that novel insights into the heterogeneity of patient responsivity to anxiolytics may be obtained by comparing the efficacy of distinct classes of drugs (e.g. SSRIs and ketamine) on anxiety states with different aetiologies, but of known origin. Hence, we exploit our recent findings that a similar anxiety phenotype is induced by either *inactivation* of orbitofrontal cortex or *overactivation* of ventromedial prefrontal cortex (Stawicka et al, 2020, 2022) to compare the anxiolytic efficacy of citalopram and ketamine. In marmosets the human-intruder test measures the behavioural reactivity to an unfamiliar human; the human in this context being an uncertain stimulus provoking an anxiety-like response. Targeted intracerebral infusions were used to overactivate area 14 with dihydrokainic acid, a glutamate transporter (GLT-1) inhibitor, and to inactivate area 11 with the GABA-A/B agonists, muscimol/baclofen. The ability of an acute, systemic dose of 10 mg/kg citalopram or 1 mg/kg ketamine to ameliorate the anxiety induced by these two contrasting prefrontal interventions was then determined. Anxiety-like behaviour induced specifically by overactivation of area 14, but not that induced by inactivation of area 11, was ameliorated by citalopram. Preliminary findings demonstrate that this anxiolytic effect can be replicated by local application of citalopram into area 14. In contrast, systemic ketamine showed no systematic differences in anxiolytic efficacy between the two prefrontal manipulations, but individual variation was more prominent. We argue that these results inform our understanding of the neurobiological heterogeneity underlying anxiety. In addition, the evidence that different faces of anxiety are differentially responsive to distinct classes of anxiolytics offers potential for improved treatment strategies.

Disclosures: K.G. Mulvihill: None. **L. McIver:** None. **A.C. Roberts:** None.

Poster

PSTR293. Emotion: Investigations in Non-Human Vertebrates

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.06/PP8

Topic: G.04. Emotion

Support: MR/V033492/1

Title: Causal contribution of bilateral and left dorsolateral prefrontal cortex inactivation to heightened anxiety in the common marmoset

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Abstract: Area 25 of subcallosal cingulate cortex (scACC-25) and dorsolateral prefrontal cortex (including area 46; dlPFC-46) are consistently reported by functional neuroimaging studies to be dysregulated in depression and anxiety. scACC-25 displays overactivity, whilst dlPFC displays reduced activity, particularly in the left hemisphere. Both regions have become targets for brain intervention therapies; scACC-25 a target for deep brain stimulation for treatment-resistant depression and dlPFC, especially on the left, for high frequency transcranial magnetic stimulation in both anxiety and treatment resistant depression. Moreover, success of the latter is predicted by the extent that activity between dlPFC and scACC-25 is negatively correlated. Recently we have provided direct causal evidence for the role of scACC-25 overactivation in the enhanced reactivity to uncertain threat in a non-human primate, the common marmoset, relevant to our understanding of anxiety (Alexander et al., 2018). However, any causal role for dlPFC in anxiety has not yet been established. Thus, our current objective was to determine the existence of such a relationship by investigating the effect of inactivating dlPFC-46 in the common marmoset on anxiety-like behaviour assessed by the human intruder test of uncertainty. Marmosets (n=7, 3 females) received cannulae targeting dlPFC-46 and temporary inactivation was induced by infusion of a cocktail of GABA-A/B agonists , muscimol/baclofen (0.1mM/1mM, 0.5ul). Not only were the effects of bilateral inactivation determined but also the effects of unilateral inactivation, given the evidence of asymmetry within this region in human emotion regulation and affective disorders. Findings reveal that, similar to overactivation of scACC-25, bilateral inactivation of dlPFC-46, as well as inactivation of area 46 in the left (but not right) hemisphere alone, increased anxiety-like behaviour. This provides causal evidence for reports in the clinical literature of reduced activity in particular in left dlPFC, and aligns with previous findings in our lab showing decreased activity in left dlPFC-46 following scACC-25 overactivation.

Disclosures: R. Banai Tizkar: None. **L. McIver:** None. **C.M. Wood:** None. **A.C. Roberts:** None.

Poster

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Program #/Poster #: PSTR293.08/PP9

Topic: G.04. Emotion

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Title: Gabaergic inputs to pomc neurons are modulated by chronic unpredictable stress

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Abstract: Chronic stress exposure induces maladaptive behavioral responses and increases susceptibility for neuropsychiatric conditions. However, specific neuronal populations and circuits that are affected by chronic stress to drive maladaptive behaviors remain to be identified. We have recently shown that chronic unpredictable stress (CUS) for 10 days induces hyperactivity of proopiomelanocortin (POMC) neurons in the arcuate nucleus (ARC) and behavioral deficits such as anhedonia and behavioral despair (Fang, Chen et al., Mol Psychiatry 2021). The increased hyperactivity of POMC neurons is the result of a decrease in synaptic inhibition and an increase in intrinsic excitation. Neurons in the dorsomedial hypothalamus (DMH) provide a major source of inhibitory synaptic inputs to POMC neurons (Rau and Hentges, J Neurosci. 2019). The aim of the current study was to investigate the role of GABAergic neurons in the DMH in modulating synaptic inhibition of POMC neurons during chronic stress. Vgat-ires-Cre mice were injected with AAV-DIO-mCherry in the DMH to label GABAergic neurons. After 10 days of CUS, we recorded spontaneous firing rates and membrane potentials of GABAergic neurons in the DMH. Our data indicated that CUS decreases spontaneous firing of GABAergic neurons in the DMH. Furthermore, we have generated Vgat-ires-Cre;POMC-GFP mice to examine whether stimulation of GABAergic neurons in the DMH can attenuate the CUS-induced hyperexcitability of POMC neurons. By investigating the interactions between GABAergic neurons in the DMH and POMC neurons in the ARC, our study will identify the upstream inhibitory neurocircuits driving hyperactivity of POMC neurons during chronic stress.

Disclosures: Y. Chen: None. **X. Lu:** None.

Poster

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Topic: G.04. Emotion

Support: Japan Science and Technology Agency

Title: Characteristics of neuronal responses to complex visual stimuli in the monkey ventromedial prefrontal cortex.

Authors: *M. TOTSUKA[1], H. IWAOKI[2], N. KONOIKE[3,4], S. MIYACHI[4], K. NAKAMURA[4]; [1]Grad. Sch. of Sci., Kyoto Univ., Inuyama, Japan; [2]Natl. Inst. for Quantum Sci. and Technol., Chiba, Japan; [3]Hakubi Center, Kyoto Univ., Kyoto, Japan; [4]Ctr. for the Evolutionary Origins of Human Behavior, Kyoto Univ., Inuyama, Japan

Abstract: Appropriate evaluation of visual information about the external world is essential for survival. The ventromedial prefrontal cortex (vmPFC) has been focused on as an important brain region that links sensory information to emotional responses and processes reward or affective information. Anatomically, the vmPFC have reportedly rich reciprocal connections with the amygdala and the inferior temporal lobe. The amygdala is involved in emotional processing. In the primate species, the amygdala neurons respond to visual stimuli with emotional information. The inferior temporal lobe is the final stage in visual information processing. Given these anatomical insights, the vmPFC is considered important for integrating visual and emotional information. However, there are few studies on visual processing in the vmPFC, especially in areas 25, 14 and 10. Therefore its functions are still unclear. To elucidate how and what visual information the vmPFC neurons process, we recorded the activity of single neurons from two male Japanese monkeys (*Macaca fuscata*, both six years old). We examined the neuronal responsiveness to the complex visual stimuli while the monkey observed these stimuli. All experiments were approved by the Animal Experimentation Committee of the Center for the Evolutionary Origins of Human Behavior, Kyoto University. We prepared five categories of stimuli of behavioral significance to the monkeys; monkey faces, monkey hips, snakes, foods, and artificial objects. In total, the activity of 415 vmPFC neurons was recorded. Of these, 271 neurons (65%) showed a significant change in activity in response to the stimuli. Among these, about three-fourth (202 neurons) exhibited responses selective for certain stimuli. More than 40% of the selective neurons showed the maximal response to monkey faces or hips. The present results suggest that the vmPFC neurons conveyed visual information about conspecifics especially important for their social behavior.

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Poster

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Program #/Poster #: PSTR293.10/PP11

Topic: G.04. Emotion

Support: iMind center

Title: Distribution of Oxytocin and Vasopressin cells in the developing mouse brain and influence of early life stress.

Authors: *M. HABART[1], A. SOUMIER[2], G. LIO[3], C. DEMILY[5], A. SIRIGU[4];
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Abstract: Oxytocin and vasopressin are two neuropeptides involved in social behavior. Although the anatomy of these systems is known, few studies have focused on their maturation across developmental stages. We implemented a 3D developmental atlas based on 3D imaging of cleared and oxytocin and vasopressin immunostained mouse brains at 5 postnatal ages (P0, P3, P7, P14, P56). We found that the number of oxytocin cells doubles during development while no changes were observed for vasopressin neurons. We also found no sex effect during development. The increase of oxytocin cell number is expressed in selective regions such as the paraventricular and the periventricular nucleus and in a newly referenced oxytocin selective region, we named antero-lateral preoptic area. Cell density analyses in the PVN revealed the existence of two oxytocinergic clusters, one postero-dorsal present from birth and another located in the antero-ventral axis developing later. These results suggest that the wiring of the social brain relies on integrated communication between the activity of stable (vasopressin) and flexible, experience-dependent (oxytocin) neural networks. In a further study we investigated plasticity of oxytocin and vasopressin neurons in a context of early stress following maternal separation. We found a significant effect on oxytocin cell number only at a later stage of development (P14) and again no difference for the vasopressin system. All together these findings show that the hypothalamic oxytocin system develops in the postnatal life and that the impact of stressful events on this circuit appear at a later stage. Overall, these results show that the hypothalamic oxytocin system develops during postnatal life and that the impact of stressful events on this circuit appears at a later stage of brain maturation.

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Poster

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Title: Neurogenesis-dependent effects of electroconvulsive shock require mGluR2

Authors: *A. SANTIAGO[1,2], J. CASTELLO SAVAL[2], V. M. LUNA[2,3], H. CHUNG[2], R. HEN[2], W.-L. CHANG[2];
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Abstract: Therapeutic use of electroconvulsive shock (ECS) is 70%-80% effective for the remission of treatment-resistant depression. Yet the question of how ECS produces these powerful effects remains unanswered. Like other more common forms of antidepressant treatment such as fluoxetine, ECS has been shown to increase neurogenesis in the hippocampal dentate gyrus of rodent models. In human subjects, structural MRI of patients with depression reveals an increase in dentate gyrus volume after ECS treatment, as compared to volume before treatment, and the increase in dentate gyrus volume correlated with symptom improvement. Yet the question of how ECS-induced neurogenesis supports improvement of depressive symptoms remains unknown. Here, we show that ECS-induced neurogenesis is necessary to improve depressive-like behavior of mice exposed to chronic corticosterone. We then use slice electrophysiology to show that optogenetic stimulation of adult-born neurons produces a hyperpolarization in mature granule neurons. We identify that this hyperpolarization requires the activation of metabotropic glutamate receptor 2 (mGluR2). Consistent with this finding, we observe reduced expression of the immediate early gene cFos in the granule cell later of ECS vs sham subjects. Finally, we use conditional expression of mGluR2-shRNA virus to knockdown mGluR2 expression specifically in mature granule neurons. We find that mGluR2 knockdown prevents anti-depressant-like behavioral effects of ECS. Together, these findings reveal the importance of mGluR2 both in the suppression of mature granule neuron activity and in the therapeutic effect of ECS.

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Poster

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Title: Activation of the claustrum ensemble increases anxiety levels following stress exposure

Authors: M. TANUMA[1], Y. YOKOYAMA[1], K. MIYAJI[1], J. OHKUBO[1], R. YOKOYAMA[1], H. UENO[1], K. SEIRIKI[1], H. NOMURA[2], H. HASHIMOTO[1], ***A. KASAI**[1];
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Abstract: A subpopulation of neurons in the claustrum (CLA ensemble) is responsible for mediating anxiety responses to acute psychological stressors that elicit negative emotional states. However, the precise mechanism in which the CLA ensemble controls stress-induced anxiety responses remains unclear. To address this question, here we conducted calcium imaging by expressing GCaMP6f in the CLA ensemble in freely moving mice during behavioral tests conducted before and after stress exposure. Prior to stress, we observed that approximately 10% of the neurons in the CLA ensemble display increased calcium levels when entering an anxiogenic center zone in the open field. In the open field test following social defeat stress, a significant increase in calcium levels was observed in 10% of the CLA ensemble when mice entered the center zone, while a marked decrease in calcium levels of the subset was observed after mice exited the center zone. Longitudinal tracking analysis revealed that approximately 25% of the neurons with increased calcium levels overlapped before and after stress. In addition, we observed a significant increase of pairwise temporal correlations within the CLA ensemble during the open field test following stress compared to those before stress. Furthermore, the mice showed reduced time spent in the zone where the CLA ensemble was optogenetically activated in the open field test. These results indicate that the activation of the subset of the CLA ensemble after stress contribute to increasing anxiety levels and anxiety-related behaviors.

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Poster

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Title: Monoaminergic modulation of the Dorsal Raphe Nucleus shapes the momentary release of serotonin at Dorsal Striatum-Amygdala circuits

Authors: *L. NAVA[1], Y. PELLOUX[1], L. BONTEMPI[1], A. LOCARNO[1], N. BARSOTTI[2], M. PASQUALETTI[2], Y. LI[3], R. TONINI[1];
[1]Inst. Italiano di Tecnologia, Genova, Italy; [2]Univ. of Pisa, Pisa, Italy; [3]Peking Univ., Beijing, China

Abstract: The dorsal striatum (DS) integrates sensorimotor circuits via cortico- and thalamic inputs, and motivational inputs from the substantia nigra pars compacta (SNc), thereby

regulating voluntary movements and goal-directed control of behavior. The DS is also indirectly connected via SNc to the Central Amygdala (CeA), a brain region involved in processing both positive and negative valence stimuli. The connectional hub, formed by the sensory DS and the CeA, is shaped by the temporal dynamics of the neuromodulator serotonin (5-HT) released by projections originating from the Dorsal Raphe Nucleus (DRN). In addition to serotonergic neurons ($DRN_{5\text{-}HT}$), the DRN contains dopaminergic cells (DRN_{DA}). DRN_{DA} neurons are anatomically placed in proximity to $DRN_{5\text{-}HT}$ cells, suggesting a modulatory functional crosstalk. Anatomical evidence also shows that the DRN receives projections from the noradrenergic locus coeruleus (LC). However, how the DRN processes different monoaminergic signals to shape striatal 5-HT release remains unexplored. In this study, we combined pharmacological and optogenetic approaches ex-vivo together with fiber photometry in-vivo to examine how DRN_{DA} neurons and LC projections to the DRN (LC→ DRN) modulate the activity of $DRN_{5\text{-}HT}$ cells and the release of 5-HT in both the DS and CeA. We found that exogenous DA application in the DRN boosted the firing activity of DS- and CeA-projecting $DRN_{5\text{-}HT}$ neurons ($DRN_{5\text{-}HT}$→DS and $DRN_{5\text{-}HT}$→CeA). While this DA-mediated increase in firing activity was insensitive to dopamine D1 or D2 receptor antagonism, it was prevented by the application of the adrenaline α1 receptor (α1R) antagonist prazosin. Accordingly, in tyrosine hydroxylase (TH)-CRE mice infused into the DRN with an adeno-associated viral (AAV) vector encoding the opsin Chrimson, we demonstrated that light-activation of DRN TH^+ neurons resulted in the α1R-mediated increase of $DRN_{5\text{-}HT}$→DS or $DRN_{5\text{-}HT}$→CeA firing rate. Furthermore, in dopamine beta-hydroxylase (DBH)-CRE mice injected with a Chrimson-expressing virus into the LC, we observed that LC→CeA projections preferentially activate DRN_{DA} neurons compared to $DRN_{5\text{-}HT}$ cells. By using genetically encoded sensors for monitoring the temporal dynamics of 5HT signal, we found that exogenous DA infusion in the DRN, as well as the optogenetic activation of either DRN_{DA} neurons or LC DRN, results in 5-HT release in the DS and CeA. In summary, our results indicate that monoaminergic modulation of the DRN microcircuit promotes concomitant 5-HT release in the DS and CeA, thus increasing our understanding of how emotional states can influence voluntary movement.

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Poster

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Title: The amygdala enkephalin system controls emotional recuperation following aversive experiences

Authors: *N. GUNGOR, Y. ISHIZU, N. JOSE, J. P. JOHANSEN;
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Abstract: Aversive experience and recuperation from it can be seen as interlinked processes which collectively define negative encounters inducing fear and anxiety. Despite this fact, the neural mechanisms mediating recuperation have not been studied. We define recuperation as an internal state, triggered by aversive experiences, which helps animals cope with dangerous environments by reconstituting their emotional well-being. Using a wide range of aversive behavioral assays combined with chemogenetic and in-vivo microendoscopic imaging, we examined the role of enkephalin expressing cells in the central nucleus of the amygdala (CeA-ENK) on recuperation in adult male and female mice. We discovered that chemogenetic inhibition of CeA-ENK cells reduces recuperation across different aversive behavioral assays. Single-cell in vivo calcium imaging showed that a proportion of CeA-ENK cells respond to aversive stimuli such as noxious hotplate, foot shocks and tail suspension. Importantly, separate populations of CeA-ENK cells are active during aversive events or homecage rest periods following these experiences. Furthermore, we studied the afferents, efferents as well as immuohistochemical characteristics of CeA-ENK cells. Cortical, hippocampal, olfactory and extended amygdala inputs dominate the afferents, whereas posterior brain regions located in midbrain, pons and medulla, as well the bed nucleus of stria terminalis are major targets of CeA-ENK inputs. We found that moderate and low proportion of CeA-ENK cells expresses calcitonin gene related peptide receptor and PKC delta, respectively. These results demonstrate the central role of the CeA-ENK system in facilitating recuperation from aversive experiences and suggest new treatment approaches for mitigating the effects of trauma.

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Poster

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Title: Single cell activity of serotonergic neurons in the dorsal raphe nucleus during emotional behaviors

Authors: G. E. PAQUELET, K. CARRION, C. O. LACEFIELD, P. ZHOU, R. HEN, ***B. MILLER**;
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Abstract: The serotonin system regulates a vast array of emotional behaviors that span the spectrum from positive valence to negative valence. To determine the firing properties of serotonergic neurons during emotional behaviors, we adapted miniature microscopy to serotonergic neurons in the dorsal raphe nucleus (DRN-5HT). We imaged calcium activity in over 2,000 genetically identified DRN-5HT neurons across a range of emotional behaviors spanning positive and negative valence. These behaviors encompassed several modalities and categories including gustatory, auditory, innately threatening stimuli, foot shock, social interaction, and emotional learning. As comparators, we also recording DRN-5HT activity during exposure to neutral stimuli across several modalities. We found: 1. Across the population, DRN-5HT neurons are far more activated by valenced stimuli (positive or negative) compared to neutral stimuli. 2. Most DRN-5HT neurons have habituating responses over repeated presentations of valenced stimuli (but stable activity to neutral stimuli). 3. DRN-5HT responses to innately neutral stimuli increase after neutral stimuli take on valence through associative conditioning. 4. Within a given modality (eg gustatory), individual neurons respond to the intensity of the stimulus (salience) rather than the absolute valence of the stimuli. 5. Most DRN-5HT show mixed selectivity, responding to several emotional stimuli (but not all) across valence in combinations consistent with random assortment. 6. However, at the extreme ends of valence and modality (e.g. sucrose and shock) DRN-5HT neurons show more selectivity than expected by chance. 7. There are many ensembles of highly correlated DRN-5HT neurons, with tightly matched activity over long timescales even in the absence of specific extrinsic stimuli. We then investigated the single cell activity of DRN-5HT that project to specific targets (VTA and BNST). We found that: 1. DRN-5HT->VTA neurons and DRN-5HT->BNST neurons are non-overlapping and reside in different areas of the DRN. 2. Both projections include DRN-5HT cells that respond to all emotional stimuli we tested (there is no strict segregation between projections). 3. However, the proportion of cells varied, with the DRN-5HT->VTA projection containing more cells that respond to sucrose, and the DRN-5HT->BNST containing more cells that respond to threat. This large-scale study of DRN-5HT responses shows that the DRN-5HT system responds to emotional salience using ensembles with mixed selectivity and biases in downstream connectivity.

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Poster

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Title: Neuromodulation as a mechanism for lifelong learning in the prefrontal cortex

Authors: *K. BATRA[1,2], C. N. YI[1,2], T. ROY[1,2], M. G. CHAN[1,3], K. CHANG[1,2], A. BAKHTI-SUROOSH[1,2], J. YIU[1,2], C. R. LEE[1,2], R. WICHMANN[1], C. JIA[1,2], B. TSUDA[1,2], T. J. SEJNOWSKI[1,2], K. M. TYE[1,2,3,4];
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Abstract: Cognitive flexibility allows the brain to adapt to different contexts by enabling complex phenomena like transfer learning, task-switching and lifelong learning. The prefrontal cortex (PFC) has been hypothesized to contribute to this flexibility, explained by various models (Miller and Cohen, 2001) describing the population ensemble dynamics during goal-driven tasks. Further, the PFC is innervated with an abundance of neuromodulatory circuits (Dembrow and Johnston, 2014) several of which have been implicated in guiding the PFC to modulate neural dynamics across task contexts (Vander Weele et al., 2018, Cools and Arnsten, 2022). Many attempts have been made to understand the PFC population level representation of task variables (Bocincova et al., 2022, Samboerska et al., 2022) and create models for this phenomena that switch between schema and enable meta-learning (Wang et al., 2018, Tsuda et al., 2020, Vecoven et al., 2020, Soltani et al., 2021), though they have not addressed ethological tasks and are engineering driven without experimental validation. Here, we take a hybrid approach to understand the population level computations in the PFC. Experimentally, we have designed a novel seasonal foraging behavioral task for freely-moving mice evaluating different reward and punishment pairings across multiple contingency contexts to dynamically modulate their behavior appropriately. The behavioral paradigm iteratively increases the complexity of the task so that both transfer learning and multi-task inference can be assessed. We observed differences in the reward retrieval behavior between distinct contexts ($n = 4$ mice, $F(1.08,3.240)= 30.37$, $p = 0.0094$; low cost vs no cost reward context: $p=0.0223$) and recovery of similar behavior between repetitions of the same context (low cost 1 vs low cost 2: $p>0.9999$) showing their adaptability. Complementarily, on the computational side, we are developing a novel deep learning architecture, modeling the context-dependent neuromodulatory routing of information through subpopulations of the PFC to learn multi-context tasks with a hierarchical decision-making component inspired by the Mixture of Experts framework. We are using the behavioral data to inform the model and then testing its capabilities using deep reinforcement learning simulations.

Developing a model informed by the biology of the PFC would not only help propel the world of artificial intelligence further but also be a good candidate to study neuropsychiatric conditions related to neuromodulatory dysfunction in the PFC as well as to distill through new experimental paradigms by narrowing the parameter space first using simulations.

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Poster

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Simons Collaboration on the Global Brain

Title: Visualizing the Longitudinal Development of Stress-Induced Anhedonia From Representations of Valence in the PFC

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Abstract: A critical issue within the mental health field is the lack of granularity in diagnostic practices. We speculate that many distinct pathologies are currently being diagnose as the same disease, and prescribed the same treatments - and that the key to developing effective antidepressants that work for everyone, we need to first identify a strategy to differentiate

between heterogeneous conditions. Anhedonia, described as the inability to experience pleasure, is linked to a dysregulation within the medial prefrontal cortex (mPFC), which is critical for valence processing. Dopamine (DA) tightly regulates mPFC cortical activity and associated behavior and is implicated in anhedonia. However, it remains unknown how DA modulates mPFC valence-specific neuronal population activity during anhedonia. *We hypothesize that mPFC valence-encoding processes are disrupted during stress-induced anhedonia.* To test this, we implemented learned helplessness (LH) and chronic mild stress (CMS) protocols to induce anhedonia in mice. Our findings showed a significant reduction in reward consumption and sociability in LH mice (Pearson Correlation, r=-0.69, p=0.03), but not CMS mice (r=-0.16, p=0.58). Using k-means clustering, we classified consummatory anhedonia, social anhedonia, severe anhedonia, and resilient mice (k=4). Our results showed that anhedonic groups display a significant decrease in sucrose preference (ANOVA, ($F(3,20)=13.11$, $p<0.0001$; Bonferroni's, Res/Cons, $p<0.0001$,) and social preference (ANOVA, ($F(3,20)=6.55$, $p=0.0029$; Res/Soc, $p=0.037$). Next, we performed longitudinal *in vivo* 2-photon endoscopic calcium imaging and photostimulated ChrimsonR-tdTomato VTA^{DA}-mPFC inputs while measuring mPFC population activity in mice exposed to LH (n=5 mice, N=366 neurons) and CMS (n=5, N=876). Using hierarchical clustering, we observed an increase in the proportion of non-responsive valence processing neurons in LH and CMS susceptible mice. During our longitudinal analysis, we observed a significant decrease in mPFC activity during aversive trials in susceptible mice compared to resilient groups following acute exposure to CMS (Wilcoxon Rank Sum test, $p<0.05$). Interestingly, susceptible mice revealed a significant increase in activity during reward trials compared to resilient groups ($p<0.0001$), and is decodable prior to stress. These results indicate the mPFC valence encoding properties are predictive of anhedonic states. Altogether, these experiments point to the need for increased granularity in the measurement of both behavior and neural activity, as these factors can decode the induction conditions of stress-induced anhedonia.

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Poster

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Title: Amygdalostriatal transition zone neurons encode sustained valence to direct conditioned behaviors

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Abstract: In order to respond appropriately to threats in the environment, the brain must rapidly determine whether a stimulus is important and whether it is positive or negative, and then use that information to direct behavioral responses. The amygdalostriatal transition zone (ASt) is anatomically poised to play a critical role in these processes by providing a shortcut between corticolimbic and basal ganglia circuitry to mediate behavioral responses to stimuli in parallel with the amygdala. Like the amygdala, the ASt receives converging sensory input from the thalamic and cortical pathways. However, the projections of the ASt are distinct from canonical outputs of the amygdala complex, and are integrated with striatal circuits involved in action selection. Despite this intriguing circuit connectivity, the function of the ASt is almost completely unknown.
From in vivo cellular resolution electrophysiology recordings, we find that ASt neurons show robust sustained responses to negative valence stimuli (Two-tailed t-test, $p = 0.00136$, n= 223 neurons paired, 89 neurons unpaired), which are distinct from responses observed in adjacent amygdala and striatum (One-way ANOVA, $p=0.0008$, n= 280 neurons TS, 223 neurons ASt, 25 neurons CeA). We further show that photostimulation of the ASt is sufficient to drive freezing and avoidance behaviors (Two-way ANOVA, group x laser interactions, $p = 0.0023$, $p = 0.0186$, n=8 mice ChR2, n=10 mice eYFP). Using single-nucleus RNA sequencing and in situ RNA labelling we generate a comprehensive profile of cell types and gene expression in the ASt, and find the ASt is genetically distinct from adjacent striatal and amygdalar structures (n=18-25 mice, >15000 cells per brain region, >50k unique molecular identifiers per cell). We also find that the ASt has a greater proportion of neurons expressing Drd2 than neurons expressing Drd1a (Chi-square test, $p=0.0032$, n=8 mice, >8 sections per group), a unique feature compared to other regions of the striatum. Using in vivo calcium imaging, we show that that this Drd2+ ASt neuron population robustly encodes stimuli of negative valence (Two-tailed t-test, $p = 0.0026$, n=4 mice paired, 4 mice unpaired), and in loss-of-function experiments find that optogenetic inhibition of Drd2+ ASt neurons causes a striking reduction in cue-conditioned fear responses (43% decreased freezing, Paired t-test, $p=0.0145$, n=8 mice NpHR, n=9 mice eYFP). Together, our findings

identify the ASt as a previously-unappreciated critical missing link for encoding learned associations and directing behavior.

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Poster

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1R01NS120851-01A1

Title: Unilateral mid-striatal deep brain stimulation improves cognitive flexibility in rats

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Abstract: Neuromodulation of corticofugal circuits can ameliorate deficits in flexible decision-making. For example, deep brain stimulation (DBS) of the ventral internal capsule/ventral striatum (VCVS) in humans and DBS-like stimulation of mid-striatum (midSTR) in rats both improve cognitive flexibility, a component of healthy decision-making. Clinical DBS typically entails bilateral implantation of electrode leads. The rat midSTR DBS model was also developed using bilateral stimulation. However, recent work from our lab in humans suggests that unilateral DBS may be sufficient. To test this, we assessed how unilateral vs. bilateral DBS modulates cognitive flexibility. Unilateral DBS improved flexibility like bilateral DBS, with unilateral DBS being more effective in some cases. Long Evans rats (n=8) were implanted with bipolar stimulating electrodes in left and right midSTR. Rats were trained on an extradimensional set-shifting task that requires flexible decision-making to suppress prepotent responses and adjust to changing rules. After training, rats underwent a testing period where they received bilateral stimulation, unilateral stimulation (right or left) or no stimulation (OFF condition) for one hour in open field then throughout the duration of the task (eight sessions for each stimulation condition, 32 total). Reaction time (RT) and errors were quantified using a generalized linear mixed-effects model. Brains were sliced to confirm electrode placement. cFos+ neurons in

medial prefrontal cortex (mPFC) and midSTR were compared to determine regional involvement and correlations with behavior. Unilateral and bilateral midSTR DBS similarly reduced RTs without increasing errors, improving cognitive flexibility. Right unilateral stimulation resulted in the largest reduction in RTs compared to the OFF condition (~50ms, p = 5.47e-25). This was followed by bilateral stimulation (~40ms reduction, p = 2.52e-6) and left unilateral stimulation (~30ms reduction, p = 3.83e-10). These statistics are reported for rats that have completed testing at the time of the abstract submission (n=6). Further, we expect that the reduction in RTs from stimulation will correlate with cFos expression in mPFC subregions. Specifically, if stimulation delivered to one hemisphere is associated with a greater reduction in RTs compared to the other hemisphere, it is predicted that there will be more cFos+ cells in the mPFC ipsilateral to stimulation. The results of this work will clarify the circuitry involved in our midSTR DBS rat model of VCVS DBS. This model may allow optimization of stimulation parameters and brain targets to increase DBS's therapeutic efficacy.

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Poster

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Title: Unraveling the mechanistic link between repetitive mild traumatic brain injuries and maladaptive avoidance: Insights from neural synchrony

Authors: *C. J. LI, S. SIMPSON, L. BUHLER, M. R. ANGSTMAN, S. M. HU, J. L. CHANG, E. DASTIN-VAN RIJN, S. S. NAGRALE, D. J. TITUS, A. S. WIDGE;
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Abstract: Mild traumatic brain injury (mTBI) is a prevalent health issue in the United States that can result in a wide range of outcomes, with some individuals experiencing long-term cognitive and behavioral deficits. Repetitive mTBIs (RmTBIs) have the potential to worsen this damage as the initial injury increases susceptibility to further traumas, compounding the behavioral, functional, and structural deficits associated with each injury. RmTBIs commonly lead to maladaptive avoidance (i.e., excessive avoidance in the absence of threatening stimuli) which can manifest in psychiatric disorders such as PTSD, Generalized Anxiety Disorder, and Major Depressive Disorder. However, the mechanistic link between RmTBIs and the development of these neuropsychiatric disorders is poorly understood.
We hypothesized that RmTBIs would alter the functional connectivity between the prelimbic (PL) and infralimbic (IL) cortices of the medial prefrontal cortex (mPFC) and the basolateral

nucleus of the amygdala (BLA), the main regions involved in the regulation of fear and avoidance, leading to increased avoidance behavior. To study this, we utilized the platform mediated avoidance (PMA) task, a behavioral paradigm that models the balance between avoidance and approach drives. Following 4 weeks of training, we induced RmTBIs (Days 0, 3, and 7) and implanted tetrode microdrives in adult Long Evans rats. For the next 4 weeks, we recorded neural activity in the PL, IL, and BLA simultaneously during the PMA task. RmTBIs persistently increased rats' avoidance behavior, both in the presence and absence of threatening stimuli. Even when the injured animals engaged in approach behavior, they were less effective in reward seeking than they were pre-injury. Additionally, there was diminished coherence in the IL-BLA and PL-BLA circuits during approach to the reward zone following RmTBIs when compared to non-injured animals. These post-injury behavioral and electrophysiological deficits will be correlated with structural changes which will be captured using polarization sensitive optical coherence tomography.
This study may yield valuable insights into the neural and structural attributes correlated with avoidance behavior following RmTBIs and could lead to the identification of biomarkers for diagnosis and treatment. Understanding the neural mechanisms underlying maladaptive avoidance after RmTBIs has the potential to improve the quality of life for those affected by this condition.

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Poster

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Non-Invasive Neuromodulation Laboratory

Title: Phase-locked transcranial magnetic stimulation over prefrontal cortex alters cortical excitability

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Abstract: Transcranial magnetic stimulation (TMS) is an effective treatment for those suffering with treatment resistant major depressive disorder. However, 50% of TMS patients do not experience adequate improvement in depression symptoms. Adapting TMS by increasing the

engagement of target circuits may improve the outcomes for patients. One method to improve treatment protocols may be timing stimulation to endogenous alpha oscillations since this band is dominant in the prefrontal cortex. Closed loop TMS of this frequency band in the motor cortex has effects on corticospinal excitability, but it is unclear whether it has the same effect on the prefrontal cortex. Changes in excitability, and more specifically, inhibitory effects is relevant to neuromodulation therapies because dysfunction in intracortical inhibitory circuits is associated with mood disorders such as depression. The aim of this study is to examine the effect of TMS locked to negative peaks of alpha oscillations on cortical excitability within the prefrontal cortex. Seventy trials of single and paired pulse (100ms inter-pulse interval; long-interval intracortical inhibition; LICI) TMS at 120% of resting motor threshold were given to participants (n=11) before and after 5 minutes of phase locked stimulation . The Toolkit for Oscillatory Real-time Tracking and Estimation (TORTE) was used to lock to 180 degrees, and the stimulation was delivered in triplet bursts with a minimum interval of five seconds between phase-triggered bursts. Preliminary EEG data show an enhancement of single-pulse TMS evoked potentials (TEPs) post phase-locked stimulation, consistent with previously observed effects in the primary motor cortex. Phase-locked stimulation also increased LICI, as read out from paired pulse TMS. Thus, alpha phase-locked TMS may be more effective than non-phase-locked TMS at engaging intracortical inhibitory circuits, which may improve TMS' efficacy for the treatment of depression.

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Poster

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Topic: G.04. Emotion

Support: Minnesota's Discovery, Research, and Innovation Economy (MnDRIVE) initiative
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Title: Enhancing cognitive control through improved accuracy of deep brain stimulation (DBS) programming for optimal stimulation site selection

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Abstract: Precise programming of Deep Brain Stimulation (DBS) targeting the ventral internal capsule/striatum (VCVS) is critical for maximizing DBS' effectiveness in disorders such as

depression and OCD. Our recent study demonstrated the potential to replace the subjective trial-and-error method of VCVS DBS programming. We proposed an online closed-loop framework with an objective measurement obtained from the Multi Source Interference Task (MSIT), specifically using MSIT reaction time as a measure of cognitive control. We developed Bayesian optimization algorithms to systematically investigate various electrode contacts to identify those that significantly improved cognitive control. By implementing the Upper Confidence Bound (UCB1) algorithm over multiple days (in an ensemble) and selecting the optimal stimulation site using majority voting, we can recover a known optimum with an approximate accuracy of 80%. The current study presents an alternative to majority voting for ensembles, by better leveraging individual trials. We employ two primary strategies. Firstly, we implement arm pruning, which involves the removal of underperforming stimulation sites during the exploration-exploitation trade-off of the UCB1 algorithm at consecutive stages of the ensembles. Additionally, we use an A/B testing approach to compare the performance of the last two remaining stimulation sites in cases of unclear optimality. Secondly, we calculate a response surface for each individual stimulation site based on the data obtained from each stage of the ensemble. This enables the selection of the optimal stimulation site by considering the response surface, which incorporates more comprehensive information from the individual trials than the majority vote. By incorporating these strategies, we aim to achieve a more accurate approximation of the actual underlying distribution pertaining to the effectiveness of stimulating a specific site. The importance of this extended study lies in its potential to improve the accuracy and thus overall reliability of the selection process, instilling greater confidence in the selected settings for both patients and clinicians.

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Poster

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Title: Black-box optimization of cognitive control with electrical stimulation

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Abstract: Deep brain stimulation (DBS) of the ventral internal capsule/striatum (VCVS) is a promising therapy for treatment resistant psychiatric disorders. However, effective treatment depends on correct programming of stimulation parameters. This process is currently iterative, time-consuming, and reliant on noisy, subjective measures leading to inconsistent patient outcomes and months to clinical benefit. Prior work from our lab has shown that effective VCVS DBS can acutely improve cognitive control. Using psychophysical tasks, cognitive control can be estimated through trial-to-trial measures like reaction times, presenting a potential objective, rapid optimization target. Further, in unpublished work, we reverse translated this effect to Long-Evans rats performing an extradimensional set-shifting task. To use this rodent platform to demonstrate DBS optimization for cognitive control, we developed a real-time Bayesian optimizer to minimize rat reaction times on the set-shift task (n=1). In this task, rats had to shift between selecting stimuli based on side or light to receive rewards. As with prior human work, this task requires cognitive control and is thought to engage analogous circuitry. On each trial, the optimizer selects a new stimulation amplitude between 0 and 300 μA (130 Hz, 100 μs pulse-width, bilateral mid-striatum) based on a Gaussian process model with a softmax acquisition function. Within 5 sessions, the optimizer identified 150 μA as the optimal stimulation amplitude, balancing between under and overstimulation. Further offline analyses showed that the same optimal amplitude additionally minimized delays in initiating trials and maximized accuracy. These results support the feasibility of using cognitive metrics as a control signal for stimulation programming. With further development, this approach could provide a path for streamlining and expanding access of DBS and other neuromodulation therapies in psychiatric and non-motor applications.

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Title: Deep brain stimulation does not affect impulsivity but increases inter-trial behaviors in a rodent 5-choice serial reaction time task

Authors: *M. MENSINGER[1], A. WALD[2], E. M. SACHSE[3], E. M. DASTIN-VAN RIJN[4], A. E. REIMER[2,5], A. S. WIDGE[1];
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Abstract: Deep brain stimulation (DBS) may be effective for treating severe treatment resistant psychiatric disorders. DBS-responsive disorders, such as major depressive and obsessive-compulsive disorder, often involve disruptions in cortical-striatal circuitry which can affect flexible decision-making. Previously, our lab evaluated the effect of DBS delivered to the mid striatum in rats performing an extradimensional set-shifting task. Rats exhibited a decrease in reaction time without an increase in errors, attributed to increased flexibility. Additionally, stimulation increased inter-trial behavior across all response types. It can be argued the decrease in reaction time was due to impulsivity. To elucidate this, rats performed a 5-choice serial reaction time task (5-CSRTT). Long-Evans rats (n=7) were trained on a 5-CSRTT and then implanted with bilateral bipolar Plastics1 stimulating electrodes in the mid striatum. Next, rats underwent 16 experimental sessions, evenly divided between interleaved sessions of active (current-controlled biphasic stimulation, 300 µA, 130 Hz) and sham stimulation. For each session, rats were placed in an open field for one hour to allow full onset of stimulation effect, followed by performance of the 5-CSRTT. Performance was quantified by number of premature responses, and we employed a generalized linear mixed-effects model for statistical analysis. No significant differences were found between active and sham conditions regarding premature responses ($p=0.764$). Inter-trial behavior was quantified by premature, correct, incorrect, and omission response types. Significant increase in inter-trial behavior with stimulation was found across all response types ($n=3$, $p<0.001$). Mid striatum DBS during the 5-CSRTT does not increase the number of premature responses, indicating no increase in impulsivity. Therefore, increased impulsivity does not explain decreased reaction time in the extradimensional set-shifting task, supporting increased flexibility. Inter-trial behavior results also show preserved effects across tasks. These findings help to elucidate therapeutic mechanisms of DBS in cortical-striatal circuitry.

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Title: Characterization of spike activity and local field potentials in the cortico-striatal pathway during set-shifting behavior

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Abstract: The ability to make decisions appropriate to continuously changing environments is impaired in a wide range of psychiatric disorders, including depression and obsessive-compulsive disorder. Extradimensional set shifting is commonly used as a behavioral model to study that capability, in both animals and humans. The present project aimed to characterize electrophysiological activity in the prefrontal cortex (PFC) and the striatum, and then examine the associations between the spike activity, the local field potential (LFP), and the behavior while rats performed an extra-dimensional Set Shift task. Three rats were implanted with dual Neuropixel probes, covering both the dorsal and ventral sub-regions of the medial PFC and the striatum. Electrophysiological data were obtained while rats shifted between a cue-driven Light rule and a spatial Side rule to obtain food rewards. The task required five consecutive correct responses to proceed to the next rule and one test session had a total of eight rules (alternating between Light and Side rules). Spike and LFP data were compared while rats were in different cognitive states including the decision-making periods that led to correct responses versus those that led to incorrect ones. Additionally, the data were compared between the time when the rule was just changed (thus rats were uncertain of the rules and had to explore) versus the time towards the end of rule change (when rats knew the current rule). The pattern of the LFP oscillation power appeared to be distinct between the correct trials and the incorrect trials, particularly in the theta, low gamma, and high gamma bands. For instance, the power in the low gamma band increased in the PFC around the response time during the incorrect trials, while the power of the same band remained largely unchanged in the correct trials. Putative neurons that had reward outcome-dependent firing rates were also identified. Interestingly, these putative neurons coupled with the high gamma band oscillation and strongly preferred to fire action potentials during the negative phase of those oscillations. The present study should help better understanding the role of LFPs and spikes in regulating decision-making and provide insightful information on the ongoing treatment development via neuromodulation.

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Title: Whole-brain correlates of emotion processing in mice using functional ultrasound imaging

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Abstract: Emotion states are important motivators of individual experience and behavior, and identifying their neural correlates has been the subject of affective neuroscience for many years. Human imaging studies have identified brain regions implicated in subjective emotional experiences yet remain correlative in nature. Research in animal models provides insights into the precise neuronal circuit mechanisms underlying diverse emotions, but often focuses on pre-selected brain regions and individual states. Recent advances in functional ultrasound (fUS) imaging enable the investigation of whole-brain functional activity in awake and behaving mice with limited animal disturbance. In parallel, machine vision-based facial expression analyses now allow for the quantitative and dynamic tracking of emotion state in mice. Here, we combined these two pioneering techniques to start identifying whole-brain correlates of emotion states in behaving mice. We administered a variety of emotion-evoking stimuli across different sensory and contextual domains to head-fixed mice. We examined whole-brain fUS activity during emotion states such as pleasure, disgust, pain, and fear using a general linear model and multivariate pattern analysis. Emotion-related brain activity maps were distinct from those observed during periods of stimulus delivery, suggesting separate neural correlates for sensory and emotion processing. Furthermore, machine learning and latent space embedding of whole-brain fUS patterns revealed a separation of emotion state categories, and also potential dimensional representations of valence. We also identified unsolicited emotion states, defined as spontaneous occurrences of facial expressions outside the expected stimulus environment, that elicited brain activation patterns similar to evoked emotion states. Importantly, when comparing brain activity maps across diverse emotion states, we found regions selective to individual emotion states as well as regions that were involved in all emotion states. As validation of our approach, we observed strong correspondence between the fUS signal and bulk calcium activity from fiber photometry recordings in key emotion-related brain regions such as the insular cortex and amygdala. Overall, we demonstrate that the combination of facial emotion readouts with whole-brain fUS imaging in mice represents a powerful approach to revealing the neuronal correlates of emotion, which will help guide the in-depth dissection of the underlying neural mechanisms.

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Poster

PSTR293. Emotion: Investigations in Non-Human Vertebrates

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Title: Social Exclusion Modifies the Neural Representation of Physical Pain

Authors: *C. JIA[1,2], A. TRAN[1,2], F. ALOBOUDI[1,2], K. BATRA[2,1], C. R. LEE[2,1], A. BAL[2,3], A. NGUYEN[2,1], J. DELAHANTY[2,4], M. CHAN[2,4], E. SAY[2,1], R. PATEL[2], R. WICHMANN[2], L. KEYES[2,4], F. TASCHBACH[2,1], Y. LI[5], M. BENNA[1], T. PEREIRA[2], H. LI[2], K. M. TYE[2,4,1]; [1]UCSD, La Jolla, CA; [2]Salk Inst. for Biol. Studies, La Jolla, CA; [3]Johns Hopkins Univ., Baltimore, MD; [4]Salk Inst. for Biol. Studies, Howard Hughes Med. Inst., La Jolla, CA; [5]Peking Univ., Peking Univ., Beijing, China

Abstract: Social pain, the emotional pain caused by aversive experiences with one's social group, can have deleterious effects on both mental and physical health. The "pain overlap theory" proposes that the experience of social pain can overlap with and modulate physical pain. However, we do not know if a neural substrate exists where social and physical pain overlap. To address this gap, we have designed a novel Social Exclusion paradigm, in which mice are separated from their cagemates by a switchable glass divider and observe their cagemates collectively consume a reward. To control for the tones and reward delivery, we have the Tone Only control, in which there are no mice on the reward collection side of the chamber. To control for visualizing another mouse consume a reward, we have the One Mouse control, in which mice are excluded with one mouse on the other side. For the 180 mice we have included in these paradigms, each of the 60 trials for Social Exclusion, Tone Only, and One Mouse are separated into two categories (FOMO vs Fine) using a new supervised machine learning algorithm, AlphaClass, and k-means clustering. Fear Of Missing Out (FOMO) behavior, is operationally defined by mice climbing to, rearing near, or oriented towards the social group. Trials during which mice did not orient towards the social group during reward collection are termed "Fine" trials. We found that FOMO behavior is significantly elevated during Social Exclusion, compared to the Tone Only control (*P = 0.0108). After experiencing Social Exclusion, social rank is negatively correlated with a lower latency to lick, suggesting increased affective pain behaviors in dominant mice (*P = 0.004). To find the neural substrates that might mediate social exclusion-induced hyperalgesia, we are looking in the anterior insular cortex (aIC). Using microendoscopic calcium imaging with GCaMP7f, we have discovered the aIC contains neural ensembles responsive to social and physical pain. Decoding analyses reveals that after Social Exclusion, the representation of physical pain is enhanced (***P = 0.0004). To explore the role of neuromodulators in mediating a prolonged negative affective state after social exclusion, we used a fluorescent endocannabinoid sensor ($GRAB_{eCB2.0}$) during social exclusion and pain behavior. We found that during Social Exclusion only, there is a significant increase in fluorescent activity (*P = 0.0134) during Fine trials, but not during FOMO trials, or any control condition trials. Together these findings suggest social exclusion enhances the neural

representation and behavior of physical pain and the endocannabinoid system can potentially be a mechanism to bind these two types of pain.

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Poster

PSTR293. Emotion: Investigations in Non-Human Vertebrates

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Program #/Poster #: PSTR293.28/QQ1

Topic: H.10. Human Learning and Cognition

Title: Investigating the mechanisms of precise predictive timing: simulation and intracranial EEG

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Abstract: Our sensory environment is rich with repetitive stimuli that we can perceive and use to predict upcoming events. Our brains can accomplish this via temporal predictive coding, one example of which is oscillatory entrainment, in which ongoing, low frequency cortical oscillations in human EEG and MEG can become synchronized to a rhythmic stream of sensory inputs. Previous investigations have observed instances of entrainment of low frequency oscillations in the delta (1-4 Hz) band, often coupled to activity in the higher frequency beta (13-30 Hz) band. However, observations of cross-frequency interactions have recently been shown to also potentially be caused by nonsinusoidal oscillations. Here, we hypothesize that cross-frequency delta-to-beta coupling in anticipatory perception might be better explained by nonsinusoidal oscillations. Furthermore, we hypothesize that the nonsinusoidal waveforms of these oscillations are driven by the temporal coincidence of excitatory top-down and bottom-up postsynaptic currents converging onto auditory cortex. That is, these nonsinusoidal oscillations could be the product of top-down modulation of neural excitability in the auditory cortex, serving a potential mechanistic role in the precision of temporal predictions. To investigate the possible occurrence of nonsinusoidal entrained oscillations in temporal predictive coding, we designed a novel anticipatory perception task. Here, we analyze intracranial EEG data from 8 epilepsy patients performing this task. We use simulated, hypothesized top-down and bottom-up signals to select electrodes of interest. Then, we compare our cycle-by-cycle approach with traditional phase-amplitude coupling methods to investigate neural mechanisms of precise predictive timing.

Disclosures: **S. Smith:** None. **B. Voytek:** None.

Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

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Title: A thalamic ventral hippocampal pathway that supports anxiety-related behavior

Authors: *M. M. GERGUES, J. BRATSCH-PRINCE, S. HASSAN, M. LI, A. KOLANJIAN, V. S. TURNER, M. A. KHEIRBEK;
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Abstract: The hippocampus (HPC) plays an important role not only in spatial memory, but in the encoding emotionally charged environments and generating appropriate behavioral responses. Yet how and which inputs are involved in the generation of anxiety-related representations in the HPC remain unknown. Using a whole-brain, cell-type specific, anatomical screen, we identified the anterior portion of the paraventricular nucleus of the thalamus (PVT), an area implicated in the processing of salient emotional stimuli, as a putative source of anxiety-related information to the HPC. In this study, we dissect the anatomical organization of the PVT-vHPC circuit and its contribution to anxiety-related behavior using advanced tracing methods and optical approaches. We used high-throughput sequencing of genetically barcoded neurons to map the axonal projection pattern of aPVT neurons and determined the organizational principles that govern output patterns of PVT-vHPC projection neurons. In optogenetic and chemogenetic studies, we find that modulation of PVT-vHPC pathway resulted in reduced avoidance of anxiogenic compartments of conflict-based anxiety tests. Using calcium imaging, we recorded the response patterns of aPVT-vHPC neurons while also monitoring BLA-vHPC neurons, a known input that modulates anxiety-related behavior. These recording revealed differential recruitment of these two pathways during exploration of anxiogenic environments. In sum, we identify a novel role for PVT-vHPC projections in modulating anxiety-related behavior, including its anatomical architecture and how its activity compares with other known inputs to the vHPC.

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Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

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Title: Innate and learned representations of appetitive and aversive stimuli in the ventral hippocampus

Authors: *J. BIANE[1], M. LADOW[2], A. FAN[3], D. L. APODACA[4], L. Z. ZHOU[4], S. T. HASSAN[2], M. KHEIRBEK[5];
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Abstract: Emotional well being requires the ability to identify and accurately interpret positive and negative stimuli in the environment. How emotionally charged stimuli are processed and encoded by the brain, however, is not well understood. The ventral hippocampus (vHPC) plays a key role in orchestrating emotional responses, including processing stimuli with innate valence, as well as learned cues predictive of emotionally salient outcomes. Moreover, dysfunction of vHPC and its outputs is associated with a variety of mood disorders, including anxiety, depression and post-traumatic stress. Thus, understanding how emotionally charged stimuli are processed by the vHPC can provide insight into the etiology of maladaptive emotional states. Here, we used 2-photon calcium imaging to record the activity of vCA1 neurons while exposing mice to a battery of stimuli with innate or learned valence. Although neuronal activity tagging studies in vCA1 and related areas show significant overlap for neurons responsive to stimuli belonging to the same valence class, but not across valence classes (ie, valence encoding), we found little evidence for such valence encoding when stimuli from distinct sensory modalities were presented (eg, sucrose, shock, predator odor, female conspecific urine). Instead stimulus identity dominated neural representations during this time. Conversely, for stimuli within the same modality (appetitive chocolate or vanilla milk, aversive quinine or high salt solution), valence encoding was present, in addition to identity, suggestive of modality-specific processing in vCA1. Finally, as recent findings suggest that neural representations of neutral cues come to

mimic the innate representations of paired outcomes, we examined how neutral odor cues predicting sucrose, low amplitude shock or high amplitude shock were transformed in vCA1 with learning. Indeed, we found an increase in the similarity of population activity for a cue and its associated outcome following training. Notably, representations of odor cues also became more similar to one another, indicating a general salience signal is also embedded in stimulus representations. Thus, vCA1 encodes a rich repertoire of information about encountered stimuli that includes stimulus identity, associated outcome, salience/arousal, and in the case of stimuli within the same modality, valence. This multitude of information may help animals to identify, interpret and react to stimuli in an appropriate manner.

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Poster

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Program #/Poster #: PSTR294.03/QQ4

Topic: G.04. Emotion

Support: NIMH-R01MH108623

Title: Control of anxiety states and underlying neural dynamics by respiratory rhythms

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Abstract: An animal's emotion state is strongly influenced by the state of its body. For example, changes in heart rate or breathing rhythms can influence how the brain responds to emotional stimuli and generates adaptive behaviors. In humans, it is well documented that changes in respiration occur during high anxiety states, and that individuals suffering from certain types of anxiety disorders experience altered sensations of breathing-derived signals. Furthermore, accumulating scientific evidence supports the idea that controlled breathing can have a positive influence on an individual's mental and physical well-being. However, the underlying neuronal circuits mediating this tight coupling between the control and sensation of respiration and anxiety-related behaviors remain unknown.
To determine how respiration influences anxiety-related behaviors and their underlying neuronal dynamics, we have identified how breathing rhythms are correlated with specific behavior motifs in tests of aversive behaviors in mice. This allowed us to predict an animal's location in safe or aversive compartments based on individual breathing rates alone. In addition, calcium imaging experiments revealed that dynamic changes in breathing rates during exploration of anxiety provoking arenas were tightly correlated to activity in the central nucleus of the amygdala. Moreover, direct control of breathing patterns using chemogenetic manipulations of neuronal subpopulations in the brainstem breathing center revealed that slowing down of respiration

acutely reduces an animal's fear-related behavior. Currently we are using high-density electrophysiology (Neuropixels) to record from limbic brain regions to determine how breathing impacts the neuronal dynamics underlying distinct anxiety states.

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Poster

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Program #/Poster #: PSTR294.04/QQ5

Topic: G.04. Emotion

Support: NIH Grant MH108623

Title: Shifting balance of local inhibitory interneurons in ventral hippocampus controls approach and avoidance behaviors.

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Abstract: The ventral hippocampus (vHPC) plays a critical role in mood and anxiety-related behaviors. Information regarding the salient nature of an environment, arising from input from cortical and subcortical regions, converge in vCA1 where an output signal is routed to specific downstream targets to support appropriate behavioral selection. Indeed, activity in projection-defined vCA1 excitatory pyramidal neurons (PNs) has been shown to influence approach or avoidance behaviors depending on the target structure. At the local circuit level, activity in hippocampal PNs is regulated by a diverse pool of local inhibitory interneurons (INs), including those expressing parvalbumin (PV), somatostatin (SST), or vasoactive intestinal polypeptide (VIP). These INs differ in their electrophysiological and local connectivity patterns, placing each class in a unique position to influence vCA1 circuit output and ultimately behavior. Yet, it is not understood how these IN populations shape vCA1 output in a behavior-specific manner. Here, using a combination of population and single cell in vivo calcium imaging and optogenetics in mice, we show that PV, SST, and VIP INs are differentially modulated during multiple tests of anxiety-related behavior. High-resolution analysis of mouse behavior found that during exploratory-approach behaviors, PV and VIP IN networks were recruited, while SST IN activity decreased. Conversely, during avoidance behaviors SST INs were uniquely recruited with decreased PV and VIP IN network activity. Interestingly, increases in activity of SST INs prior to approach-avoidance decisions could be predictive of future avoidance behavior, suggesting a uniquely critical role of SST INs in shaping network activity in vCA1 to guide avoidance behavior. Consistent with this, closed-loop optogenetic silencing of SST INs during simultaneous calcium imaging of vCA1 neurons revealed that inhibiting SST INs decreased avoidance behavior and altered vCA1 network activity during approach-avoidance decisions. Together, these data reveal the competitive balance between vCA1 IN populations guides vCA1

output to drive appropriate behavioral selection during anxiety-related behaviors, highlighting unique contribution of these different inhibitory networks to behaviorally-relevant vCA1 circuit function.

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Poster

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Program #/Poster #: PSTR294.05/QQ6

Topic: G.04. Emotion

Support: ARCS Foundation
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Title: Understanding the mechanisms by which vCA1 orchestrates avoidance behavior

Authors: *R. O. O'SULLIVAN[1], J. X. BRATSCH-PRINCE[1], M. A. KHEIRBEK[2];
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Abstract: The decision to approach or avoid an external stimulus is not trivial, and execution of the appropriate action is often essential to an animal's survival. Consider the competing drives to explore a new environment in order to attain food or to stay hidden in order to avoid predation. These conflicting motivations must be weighed, and their outcomes considered so that the correct behavior is selected. The vCA1 subregion of the ventral hippocampus plays a central role in this approach-avoid calculation, as it represents experiences imbued with motivation to avoid; and manipulation of vCA1 can drive avoidance. However, while a role for vCA1 in representing salient stimuli is well documented, how it is involved in appropriate behavioral selection remains unclear. For example, we currently lack an understanding of how vCA1 orchestrates avoidance of learned cues that predict aversive outcomes. Here, we use a visually guided two-way active-passive avoidance task, to dissect the contributions of vCA1 to distinct avoidance behaviors. Using circuit manipulation tools, we demonstrate that inhibition of vCA1 improves avoidance learning. However, silencing vCA1 projections to basal amygdala, is detrimental to avoidance learning suggesting differential control of avoidance learning by distinct vCA1 output streams. Using *in vivo* calcium imaging, we are now exploring what task-relevant features are encoded by vCA1 and specific vCA1 projections, and how this information is used by downstream targets to control avoidance behavior.

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Poster

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Topic: H.02. Perception and Imagery

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Title: Reorganization of thalamocortical functional connectivity underlies loss of consciousness

Authors: *Z. HUANG, A. G. HUDETZ;
Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Background. Understanding the neural basis of consciousness and the mechanism general anesthesia are two interrelated problems. The cellular-molecular action of general anesthetics has been thoroughly studied; however, their effect on consciousness at systems level remains incompletely understood. Two mechanistic hypotheses of anesthetic-induced unconsciousness have been proposed: the disruption of corticocortical loops and the disruption of thalamocortical loops. To better understand the differential roles of the two loops, we devised a method to pinpoint the thalamic counterparts of the cortex's unimodal-transmodal functional axis. Through this approach, we examined how these counterparts undergo changes during anesthesia in comparison to the conscious awake state. **Methods.** Thirty participants (18-38 ys, 20 women) underwent fMRI during conscious baseline, loss of behavioral responsiveness induced by propofol sedation, and recovery of responsiveness. We expanded the cortical gradient analysis to identify the subcortical correlates of the principal cortical gradient. Specifically, pair-wise correlations were computed between the subcorticocortical connectivity values of each subcortical voxel and the cortical gradient values, generating a topographical map of the subcortical correlate of the cortical gradient. **Results.** Propofol-induced loss of consciousness was associated with a reorganization of thalamocortical functional connectivity along the unimodal-transmodal functional axis of the cortex, where the transmodal thalamocortical connectivity was preferentially suppressed. **Conclusions.** The results suggest that both thalamocortical and corticocortical functional connectivity are disrupted in propofol sedation, supporting the importance of both mechanisms in causing unconsciousness in humans.

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Poster

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Topic: H.02. Perception and Imagery

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Title: Functional dissociation of the individual regions involved in the hippocampal-cortical network

Authors: *X. WEI[1], P. A. ANGELI[1], R. L. BUCKNER[1,2,3];
[1]Harvard Univ., Cambridge, MA; [2]Massachusetts Gen. Hosp., Boston, MA; [3]Harvard Med. Sch., Boston, MA

Abstract: Human neuroimaging has identified a hippocampal-cortical network that includes the hippocampal formation and distributed cortical regions (here labeled DN-A based on within-individual precision network estimation; Braga & Buckner 2017 *Neuron*). DN-A comprises multiple regions established to play a role in spatial cognition (e.g., parahippocampal cortex, PHC; retrosplenial cortex, RSC) as well as distributed association regions whose roles are less clear (e.g., a specific region of dorsolateral prefrontal cortex, DLPFC). Anatomical studies in monkeys suggest that the distributed network likely arises from direct projectional anatomy including a local zone of DLPFC. Interestingly, DN-A responds when individuals are imagining spatial scenes (DiNicola et al. 2023 *J. Neurophysiol.*), raising questions about how mentalizing scenes relates to perceiving scenes and whether the multiple regions within DN-A similarly respond. Here we contrasted the response of DN-A regions to perceiving versus mentally constructing scenes. A multisession hierarchical Bayesian model estimated DN-A within 11 intensively studied individuals. Separate DN-A regions were then defined (DLPFC; inferior parietal lobule, IPL; ventromedial prefrontal cortex, VMPFC; PHC; RSC). Responses were measured during Scene Perception in a low-level 0-Back task and during effortful Scene Construction by isolating trials of an Episodic Projection task that possessed the highest levels of imagined spatial content. Result suggested that DN-A responded to both Scene Perception and Scene Construction, but subregions displayed a functional dissociation. Specifically, while PHC and RSC demonstrated preferential response to both Scene Perception and Scene Construction, the higher-order regions of association cortex (IPL and DLPFC) showed relatively higher response to Scene Construction when participants effortfully mentalized scenes. These higher-order regions were scene preferential and dissociable from control regions with domain-flexible response properties. These findings indicate a potential specialization of DN-A regions with domain-specialized higher-order association regions becoming most active when scene content is mentalized.

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Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

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Title: The hippocampus sends perceptual predictions to the cortex

Authors: *O. WARRINGTON, N. N. GRAEDEL, M. F. CALLAGHAN, P. KOK;
The Wellcome Ctr. for Human Neuroimaging, UCL Queen Square Inst. of Neurol., Univ. Col. London, London, United Kingdom

Abstract: The brain must use prior knowledge to overcome the limitations of our sensory machinery and infer the cause of incoming sensory information. This knowledge generates predictions of future sensations formed by extracting statistical regularities from the environment, including rapidly learnt associations between arbitrary stimuli. While the effects of predictions on sensory processing can be seen in the early sensory cortex (Aitken et al., 2020; De Lange et al., 2018), the mechanisms underlying the generation and communication of these predictions remain unclear. The hippocampus (HC) has been suggested as an essential region coordinating learning and exploitation of predictive relationships for perceptual inference (Barron et al., 2020; De Lange et al., 2018). Representations of predicted stimuli have been found in the HC (Clarke et al., 2022; Kok & Turk-Browne, 2018), emerging after an implicit association has been learnt (Aitken & Kok, 2022). One possibility to link these findings is that the HC generates and communicates predictions to the sensory cortex via mechanisms used in episodic memory, such as pattern completion and cortical reinstatement (Hindy et al., 2016; McClelland et al., 1995; Rolls, 2013; Treves & Rolls, 1994). Indeed, predictions could exploit the reversal of information flow between the sensory cortex and the medial temporal lobe that has been found for internally-generated information in memory (Linde-Domingo et al., 2019; Staresina & Wimber, 2019; Treder et al., 2021) and mental imagery (Dijkstra et al., 2017, 2019). However, previous studies could not determine whether the HC was responsible for passing these predictions to the cortex.
Here we collected submillimetre 7T fMRI data to measure layer-specific activity in the entorhinal cortex (EC). Layer-specific fMRI allows one to infer the direction of communication between the HC and EC, as EC layers II & III project to the HC, while layer V & VI receive feedback projections from HC. Participants performed a task in which an auditory cue predicted shapes in 75% of trials. Crucially, we omitted the expected shape on 25% of trials, thus isolating the prediction signal from the bottom-up input and allowing us to ask: In which direction are predictions communicated between the HC and neocortex? Using layer-specific informational connectivity analysis, we find that the posterior subiculum sends information specific to the predicted but omitted shapes to the deep layers of the EC. These findings demonstrate that the HC sends prediction signals to the neocortex, adding weight to the suggestion of its pivotal role in generating perceptual predictions.

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Poster

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Topic: H.02. Perception and Imagery

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Title: Illusory surface representation in visually responsive thalamic nuclei

Authors: *A. ARSENOVIC[1,2], M. KREIS[1,2], A. ISCHEBECK[1,2], N. ZARETSKAYA[1,2];
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Abstract: Kanizsa figures are visual illusions that induce perception of an illusory surface, which is defined by emerging illusory contours. Responses to illusory Kanizsa shapes can be observed not only in the temporal and parietal cortical areas, but also in early visual cortical areas such as the primary visual cortex (V1). Specifically, there is a signal increase within the topographic representation of an illusory surface. Predictive coding theory explains this signal enhancement through a mismatch between the bottom-up sensory input and the top-down prediction, termed prediction error. Here, we investigated whether visual subcortical regions are also capable of representing illusory content by examining the topographically specific responses to illusory shapes in the lateral geniculate nucleus (LGN) and the inferior pulvinar nucleus of the thalamus using functional MRI. 32 healthy human participants (male = 20, female = 12; age: 18-33, $M = 23.59 \pm 3.04$) took part in the experiment. Participants were instructed to perform one of the two symbol detection tasks (color or symbol identity), during which six flickering circle segments appeared on the screen. The circle segments were oriented such that they either formed an illusory square on one side of the central fixation task or did not form an illusory figure (inverted outwards). Additionally, we presented participants with a functional localizer experiment consisting of a flickering checkerboard located either at the surface representation of the illusory squares or at the background surrounding the squares. This allowed us to define voxels in each area representing illusory surface only. We tested for the presence of illusory surface responses, their topographic specificity and their modulation by task difficulty in the LGN and the inferior pulvinar, including V1 for comparison. Similarly to V1, regions representing the surface of the illusory squares in the LGN as identified by the localizer showed an increased response to illusory Kanizsa squares. This response was contralateral to the illusory surface presentation. Pulvinar also showed an overall increased response to illusory Kanizsa squares, but no spatial specificity with regard to laterality of illusory surface. Illusory responses of all three areas were not affected by task difficulty. These results demonstrate that visually responsive thalamic nuclei can represent illusory shapes in a way that is consistent with predictive coding theory. They are also in line with previous studies showing LGN's contribution to higher-level visual processing.

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Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.10/QQ11

Topic: G.04. Emotion

Support: CIHR

Title: Sources of monosynaptic input to neurons of the paraventricular nucleus of the thalamus that project to the shell of the nucleus accumbens and central extended amygdala

Authors: S. LI, S. LI, *G. J. KIROUAC;
Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: The paraventricular nucleus of the thalamus (PVT) sends dense projections to the shell of the nucleus accumbens (NAcSh) and the central extended amygdala composed of the dorsolateral region of the bed nucleus of the stria terminalis (BSTDL) and the lateral region of central nucleus of the amygdala (CeL). Projection specific modulation of these efferent pathways has been shown to regulate appetitive and aversive behavioral responses. The present investigation applied an intersectional monosynaptic rabies tracing approach to quantify the brain-wide sources of afferent input to PVT neurons that primarily project to the NAcSh, BSTDL and CeL as identified by microinjections of an adeno associated virus that transduces Cre recombinase in the retrograde direction. The prefrontal cortex and the ventral subiculum of the hippocampus were major sources of input to the PVT projection neurons. A number of hypothalamic and brainstem regions associated with homeostasis and regulation of body state were also found to be significant sources of input to the projection neurons. These included the dorsomedial, ventromedial, and arcuate nuclei of the hypothalamus and the periaqueductal gray matter, lateral parabrachial nucleus, and nucleus of the solitary tract of the brainstem. Other important sources of input were the thalamic reticular nucleus, lateral septal nucleus, medial preoptic area, and subfornical organ. Analysis of regional sources of afferent input shows that PVT neurons that project to the NAcSh, BSTDL, and CeL receive the largest proportion of its inputs from the limbic cortical areas and the hypothalamus. Neurons in limbic cortical areas are postulated to transmit signals related to the saliency of stimuli and their context to PVT projection neurons that regulate behavior. In addition, hypothalamic and brainstem inputs are proposed to transmit signals related to homeostasis and body state to these same neurons. Recent observations that PVT neurons have axons that bifurcate extensively to divergently innervate the NAcSh, BSTDL and CeL in addition to limbic cortical regions and the hypothalamus suggest that the PVT broadly coordinates neural activity in brain regions that mediate behavioral responses. A convergence-divergence arrangement of inputs and outputs underscores the accumulating evidence that the PVT regulates many types of behavioral responses.

Disclosures: S. Li: None. **S. Li:** None. **G.J. Kirouac:** None.

Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.11/QQ12

Topic: G.04. Emotion

Support: National Research Foundation of Korea, 2020R1A2C1014372
National Research Foundation of Korea, 2017M3C7A1029609

Title: The dorsal hippocampus-medial prefrontal cortex circuitry regulates behavioral despair

Authors: S. YOON, G. CHUNG, W. SONG, S. KIM, ***M.-H. KIM**;
Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Despair is a core symptom of depressive disorders. However, little is known regarding neural circuits mediating despair and their modulation by antidepressants. Here, we show that neural activity in the dorsal hippocampus (dHP) affects behavioral despair through the projections to the medial prefrontal cortex (mPFC). The antidepressant ketamine rapidly induced anti-despair-like behaviors and enhanced c-Fos expression in both the dorsal and ventral hippocampi. Knockdown of $GABA_A$ receptor gamma 2 subunit gene (Gabrg2) or DREADD-mediated suppression of interneurons in the dHP CA1 area induced anti-despair-like behaviors in mice. Conversely, pharmacological and chemogenetic potentiation of GABAergic transmission in dHP CA1 neurons induced despair-like behaviors. Trans-synaptic tracing of dorsal CA1 neurons with wheat germ agglutinin (WGA)-Cre revealed a monosynaptic connection between the dorsal hippocampus and mPFC. Optogenetic stimulation of CA1 neurons in the dHP induced spike firing and increased c-Fos expression in the mPFC neurons. In addition, the chemogenetic activation of mPFC neurons in the dHP-mPFC circuitry reversed the behavioral despair induced by the activity suppression of the CA1 pyramidal neurons in the dHP. Collectively, these results indicate that neuronal activity in the dHP modifies behavioral despair and contributes to the antidepressant effects of ketamine through the dHP-mPFC circuitry.

Disclosures: S. Yoon: None. **G. Chung:** None. **W. Song:** None. **S. Kim:** None. **M. Kim:** None.

Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.12/QQ13

Topic: G.04. Emotion

Support: NIH Grant MH114112
NIH Grant MH114831

Title: Connectional architecture of a mouse hippocampal circuit node controlling stress-induced anxiety responses

Authors: *J. SUN, I. BOWMAN, D. LO, T. BOESEN, M. RUDD, L. GOU, C. CAO, J. GONZALEZ, B. ZINGG, L. GARCIA, S. YAMASHITA, K. MORADI, S. NANDA, Q. ZHAO, N. FOSTER, H. HINTIRYAN, H. DONG;
Neurobio., UCLA, Los Angeles, CA

Abstract: The role of the ventral subiculum (SUBv) in mediating psychological stress coping has been widely acknowledged. However, it still remains unclear for how different neuron types in the SUBv are affected by psychological stress. To address this long-standing question, we inject fluorescent retrograde tracers into different projection targets of the SUBv to label its different populations of projection neurons (PNs). Thereafter, the same group of mice were exposed to acute restraint stress. Using c-fos as neuronal activation marker, we found that PNs neurons in the SUBv activated by acute restraint stress projected to various regions, including the nucleus accumbens (ACB), anterior hypothalamic nucleus (AHN), lateral septal nucleus (LS), and bed nuclei stria terminalis (BST). To validate these findings, we employed a knock-in mouse model featuring activity-dependent genetic labeling (TRAP2) and confirmed the engagement of ACB- and AHN-projecting PNs during acute restraint stress. Additionally, through unbiased collateralization mapping experiments, we found that a subset of SUBv neurons concurrently targeted multiple areas, such as the ACB and AHN. Furthermore, we also characterized neural inputs to stress-activated neurons in SUBv, such as the medial septal nucleus (MSN) and lateral preoptic area (LPO). Finally, in TRAP2 mice, we conducted chemogenetic activation of the SUBv neuronal ensemble, which was tagged by acute restraint stress, leading to the elicitation of anxiety-related behaviors. Conversely, silencing the SUBv ensemble attenuated anxiety-related behaviors induced by restraint stress. These findings highlight the significance of the stress-responsive inputs and outputs of SUBv in unraveling the neural circuitry underlying stress-induced anxiety responses.

Disclosures: J. Sun: None. **I. Bowman:** None. **D. Lo:** None. **T. Boesen:** None. **M. Rudd:** None. **L. Gou:** None. **C. Cao:** None. **J. Gonzalez:** None. **B. Zingg:** None. **L. Garcia:** None. **S. Yamashita:** None. **K. Moradi:** None. **S. Nanda:** None. **Q. Zhao:** None. **N. Foster:** None. **H. Hintiryan:** None. **H. Dong:** None.

Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.13/QQ14

Topic: D.05. Auditory & Vestibular Systems

Support: DFG Grant KO 987/14-1

Title: Deviance detection in subthalamic neural population responses to natural stimuli in bats

Authors: *J. WETEKAM, J. HECHAVARRIA, L. LÓPEZ-JURY, E. GONZÁLEZ-PALOMARES, M. KÖSSL;
Goethe-University Frankfurt, Frankfurt am Main, Germany

Abstract: Deviance detection describes an increase of neural response strength caused by an improbable acoustic stimulus. This ubiquitous phenomenon has been reported for multiple species, from subthalamic areas to auditory cortex. While cortical deviance detection has been well characterised by a range of studies covering neural activity at population level (mismatch negativity, MMN) as well as at cellular level (stimulus-specific adaptation, SSA), subcortical deviance detection has been studied mainly on cellular level in the form of SSA. Here, we aim to bridge this gap by using noninvasively recorded auditory brainstem responses (ABRs) to investigate deviance detection at population level in the lower stations of the auditory system of a hearing specialist: the bat *Carollia perspicillata*. Our present approach uses behaviourally relevant vocalisation stimuli that are closer to the animals' natural soundscape than artificial stimuli used in previous studies that focussed on subcortical areas. We show that deviance detection in ABRs is significantly stronger for echolocation pulses than for communication calls or artificial sounds, indicating that subthalamic deviance detection depends on the behavioural meaning of a stimulus. Additionally, complex physical sound features like frequency- and amplitude-modulation affected the strength of deviance detection in the ABR. In summary, our results suggest that at population level, the bat brain can detect more complex violations of regularity than simple frequency changes already in the brainstem. To achieve this, neural populations integrate different features of the input, exhibiting more complex forms of deviance detection than single neurons in subthalamic brain areas.

Disclosures: J. Wetekam: None. **J. Hechavarria:** None. **L. López-Jury:** None. **E. González-Palomares:** None. **M. Kössl:** None.

Poster

PSTR294. Subcortical Circuitry of Perception and Emotion

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.14/QQ16

Topic: G.04. Emotion

Title: Encoding valence and arousal in the human brain; amygdala stimulation drives a circuit activating the anterior cingulate cortex

Authors: *P. M. KASKAN[1], S. BEKER[1], J. I. BERGER[3], C. K. KOVACH[4], E. N. ESKANDAR[2], H. OYA[5];
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Iowa, Iowa City, IA; [4]Neurosurg., Univ. of Iowa, Iowa City, NY; [5]Univ. of Iowa Hosp. and Clinics, Univ. of Iowa Hosp. and Clinics, Iowa City, IA

Abstract: Using intracranial electrical stimulation of the amygdala in humans to drive a circuit including the anterior cingulate cortex, we sought to experimentally determine how the amygdala and cingulate interact during the appraisal of, autonomic responses to, and choices between alternative affective stimuli. Human subjects undergoing intracranial recordings for the treatment of drug-resistant epilepsy viewed and rated a luminance-balanced set of affective images on scales of valence and arousal. Valence ratings were used to curate 2-alternative, forced-choice trials per-subject that varied parametrically by valence difference (i.e. conflict). We collected eye movement data and pupillometric responses during the Viewing and Rating task and the Affective Choice task during neural recordings. In the Affective Choice task, choice reaction times (RTs) varied as a function of conflict (i.e. valence difference). Choice RTs on conflicting trials were significantly slower than those on non-conflicting trials. We found a weak effect of the overall valence of the choice pair on RT, with low valence offers slowing RT to a greater degree than high valence offers. To pursue the role of the amygdala in the appraisal of, autonomic responses to, and choices between alternative affective stimuli, we used an electrical stimulation fMRI (es-fMRI) database to identify areas activated by amygdala stimulation, and to confirm the amygdala's role in driving inputs with the identified stimulation parameters. fMRI analyses indicated amygdala stimulation increased blood-oxygen level dependent (BOLD) responses in large portions of the anterior cingulate, and to a lesser spatial extent, the orbitofrontal cortex. Using the same amygdala stimulation parameters, we delivered stimulus-locked and decision-locked stimulation to the amygdala during the Viewing and Rating task and the Affective Choice task to determine the role of the activated amygdala-cingulate circuit on the appraisal of affective stimuli and how such stimuli influence action control during decisions.

Disclosures: P.M. Kaskan: None. **S. Beker:** None. **J.I. Berger:** None. **C.K. Kovach:** None. **E.N. Eskandar:** None. **H. Oya:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.01/QQ17

Topic: G.06. Anxiety Disorders

Support: Nu Rho Psi Undergraduate Research Grant
Richard Barber Interdisciplinary Research Program
Undergraduate Research Opportunities Program (UROP)

Title: "mind in motion": exploring the impact of acute physical activity and mindful meditation on anxiety and endocannabinoid levels in youth

Authors: *M. MATSKO[1,2], S. ROGERS[4], C. KOWALSKI[4], J. EVANSKI[2], P. ARVIDSON[4], S. DESAI[2], A. BHOGAL[2], C. ZUNDEL[2], L. GOWATCH[2], S. ELY[2], M. SHAMPINE[2], K. MADDIPATI[3], J. BARCELONA[4], H. MARUSAK[2];
[1]Wayne State Univ., Detroit, MI; [2]Psychiatry and Behavioral Neurosciences, [3]Pathology and Lipidomics Core Facility, Wayne State Univ. Sch. of Med., Detroit, MI; [4]Ctr. for Hlth. and Community Impact, Col. of Education, Wayne State Univ., Detroit, MI

Abstract: Introduction: The positive effects of exercise and meditation on mental health are widely recognized. Previous studies in adult and animal models have indicated that acute exercise leads to increased levels of circulating endocannabinoids (eCBs), potentially explaining the observed mental health benefits such as anxiety reduction. However, the impact of acute exercise and meditation on eCBs in youth remains unexplored. Given that mental health issues often emerge during childhood and adolescence, which coincides with developmental changes in eCB signaling, investigating this relationship is crucial.
Methods: In this randomized controlled trial, data were collected from 36 youth (50% female, aged 9-17) as part of an ongoing study in the Metro Detroit area. Participants were randomly assigned to one of three 30-minute conditions: (1) moderate-intensity treadmill exercise (N=15), (2) light-intensity stretching (N=12), or (3) seated meditation (N=9). State anxiety and circulating eCB concentrations were measured before and after the condition.
Results: Significant reductions in anxiety scores were observed from pre-session to post-session across all three conditions ($p<0.002$). However, there were no significant main effects of condition, nor significant time by condition interaction on anxiety scores ($p=0.82$). While anandamide, an eCB, exhibited higher concentrations after the treadmill exercise, these differences did not reach statistical significance ($p>0.05$).
Discussion: Our findings highlight that both light and moderate-intensity exercise, along with meditation, are associated with decreased state anxiety in youth. While the differences in circulating eCBs did not reach statistical significance, preliminary analyses suggest a potential elevation in eCB levels following moderate-intensity exercise. Physical activity and meditation could serve as low-cost, low-risk behavioral interventions in conjunction with pharmacotherapy or psychotherapy for addressing mental health issues in young individuals.

Disclosures: M. Matsko: None. **S. Rogers:** None. **C. Kowalski:** None. **J. Evanski:** None. **P. Arvidson:** None. **S. Desai:** None. **A. Bhogal:** None. **C. Zundel:** None. **L. Gowatch:** None. **S. Ely:** None. **M. Shampine:** None. **K. Maddipati:** None. **J. Barcelona:** None. **H. Marusak:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.02/QQ18

Topic: G.06. Anxiety Disorders

Support: PRODEP Grant TCLL-511-6/2020-8632
CONACYT ARM 1227361

Title: The effect of a psychoeducational session on stress and treatment adherence in patients with breast cancer.

Authors: A. RODRIGUEZ-MONTERO[1], R. CASTILLO-LÓPEZ[2], **T. CIBRIAN-LLANDERAL**[1], O. GALINDO-VASQUEZ[3], *S. MORALES[2];
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Abstract: Cancer is one of the most relevant diseases today, due to its incidence, prevalence, and mortality. The diagnosis of breast cancer often presents significant challenges in various areas of life. The disease itself, events following the diagnosis, and treatments can have an impact on physical, psychological, economic, and social levels. These effects can manifest as family problems, financial difficulties, stress, anxiety, depression, fear of recurrence, among others. Additionally, it has been reported that because of the physical and emotional events faced by cancer patients, stress response mechanisms are activated, mainly in the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for releasing certain catecholamines, including cortisol. The objective of this project is to design and implement a psychoeducational session that allows for the reduction of stress levels in patients, provides them with the necessary tools to develop behaviors that promote adherence to oncological treatment, to identify the most vulnerable patient groups to prioritize their care. A descriptive, quasi-experimental study with pre-test and post-test will be conducted, consisting of two randomly assigned groups: an intervention group and a control or waitlist group. The Perceived Stress Scale (PSS-10), Measure of Current Status Scale (MOCS), and the Therapeutic Adherence Scale for Breast Cancer Patients (EAT-CaMa) will be used as evaluation instruments.
30 participants were evaluated, of which 2 were excluded because they did not meet the inclusion criteria. The Kolmogorov-Smirnov test for normality was used, and non-normal data were obtained, so the Spearman correlation test was used. The dimensions of treatment adherence from the EAT-CaMa Scale were correlated with perceived stress and the dimensions of the Measurement of Current State (MOCS) scale. The results were statistically significant between ease of relaxation and treatment side effects and physician-patient communication (P=0.048). Similarly, perceived stress showed significant relationships with coping strategy dimensions (P=0.002), self-efficacy (P=0.021), perception of social support (0.032), and assertiveness regarding needs (P=0.036). The perception of attention from others showed significant results in relation to self-efficacy (P=0.010). These results provide important information about the relationships between the evaluated dimensions in your study and may have implications for treatment adherence and stress management in the participants

Disclosures: A. Rodriguez-Montero: None. **R. Castillo-López:** None. **T. Cibrian-Llanderal:** None. **O. Galindo-Vasquez:** None. **S. Morales:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.03/QQ19

Topic: G.06. Anxiety Disorders

Title: Novelty-based fear extinction in people with social anxiety

Authors: *L. BUDGE[1], S. SKLENARIK[1], P. LONG[1], L. KLIN[1], M. SHRESTHA[1], M. ASTUR[1], H. POSADA-QUINTERO[1], K. TREADWELL[1], D. F. TOLIN[3], R. S. ASTUR[2]; [2]Dept. of Psychological Sci., [1]Univ. of Connecticut, Storrs, CT; [3]Anxiety Disorders Ctr., Inst. of Living, Hartford Hosp., Hartford, CT

Abstract: Social anxiety disorder (SAD) has one of the highest lifetime prevalence rates of all psychological disorders (~12% in the general population; Kessler et al., 2005). If left untreated, SAD follows a chronic and debilitating course (Grant et al., 2005). Exposure, which is a key component of cognitive behavioral therapy (CBT) for SAD, has benefited greatly from our understanding of fear extinction protocols. Importantly,, not all individuals experience reduced social anxiety following the extinction phase of exposure therapy. Recent research has focused on improving extinction practices for the better long-term elimination of conditioned behaviors. One such study demonstrated that extinction efficacy could be increased by replacing a shock with a novel innocuous tone (Dunsmoor et al., 2015). However, novelty-based extinction has not been tested in populations with SAD. Accordingly, the purpose of the current study is to determine the efficacy of a novelty-based extinction model in reducing acquired fear in individuals with moderate to severe social anxiety. Twenty-seven undergraduates with moderate to severe social anxiety were recruited. Participants were conditioned to fear one of two angry faces (adapted from Dunsmoor et al., 2015) by pairing one of the faces with aversive electrical stimulation to the forearm. Participants then underwent a standard extinction protocol (shock omission) or an augmented extinction protocol (shock omission + novel tone). Reinstatement was tested after extinction. Physiological fear measures were obtained via electrodermal response and psychological aversion to the faces were obtained via a visual analogue scale. Initial analyses indicate that participants in both groups underwent similar extinction. However, during reinstatement, participants in the novelty-based extinction condition showed significantly enhanced fear reduction to the fearful face compared to participants in the standard extinction condition ($p < 0.001$). We will also report how severity of SAD correlates with these fear reductions and describe sex differences in extinction efficacy. Subsequent studies will focus on the longevity of the extinction effects and clinical implications of a novelty-based extinction process within exposure therapy procedures.

Disclosures: L. Budge: None. **S. Sklenarik:** None. **P. Long:** None. **L. Klin:** None. **M. Shrestha:** None. **M. Astur:** None. **H. Posada-Quintero:** None. **K. Treadwell:** None. **D.F. Tolin:** None. **R.S. Astur:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.04/QQ20

Topic: G.06. Anxiety Disorders

Support: NIH Grant R01MH116953

Title: Functional Connectivity of the Locus Coeruleus with Bilateral Insula is associated with increased Anxious Arousal in Anxiety Disorder and PTSD

Authors: *P. T. NEUKAM[1], S. BOUKEZZI[1], Y. JACOB[1], Y. I. WHITAKER[1], P. BALCHANDANI[2], L. MORRIS[1], J. MURROUGH[1];
[1]Psychiatry, [2]Diagnostic, Molecular, and Interventional Radiology, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Anxiety and stress related disorders are among the most prevalent neuropsychiatric conditions in the United States, with pathological anxiety symptoms such as anxious arousal and fear being core features. Preclinical studies suggest that increased tonic activation of locus coeruleus (LC), a brainstem nucleus primarily responsible for the synthesis of norepinephrine in the brain, together with other brain regions is related to anxiety related behaviors. In humans, establishing a role for the LC in pathological anxiety and linking it to clinical measures of anxiety remains a challenge due to the technical limitations of 3-Tesla MRI. Therefore, the aim of this study was to use ultra-high field 7-Tesla (7T) imaging and seed-based resting-state functional connectivity (RSFC) from the LC to the whole brain and relate the connectivity measures to anxious arousal (AA), a core feature of pathological anxiety and PTSD. Data were collected using a 7T Siemens Magnetom MRI and consisted of patients with anxiety-related (ANX) disorders (N=20), PTSD (N=13), and healthy controls (N=27). Individual LC masks were created from a magnetization transfer scan with 400μm³ resolution using an in-house developed unsupervised Gaussian mixture model machine learning algorithm for segmentation. Resting-state data were collected with 1.5 mm³ (16 subjects with 2.5 mm³) resolution, preprocessed and denoised using multi-echo independent component analysis implemented in *afni*. The LC masks were coregistered to EPI space and voxel wise Fisher-Z correlation coefficients from the LC mask to whole brain were computed for a seed-based RSFC analysis using *afni*. AA was measured with the Mood and Anxiety Symptom Questionnaire. A one-sample t-test was conducted on the group level on the correlation maps with SPM12 that included AA, gender and age as regressors. We found significant bilateral clusters RSFC of the LC with the insula (left: $p < 0.001$ k(FWE corr.); right: $p < .05$ k(FWE corr.)) that positively correlated with AA (left insula $r = 0.572$, $p = .001$, right insula $r = 0.484$, $p = .004$) in ANX and PTSD patients. There was no difference, however, between the anxiety and PTSD groups for both insula regions. This is the first study using 7T imaging to show that the strength of the functional coupling between the LC, a crucial region implicated in anxiety, and the insula, a region that has been suggested to represent anxiety sensitivity and individuals having high anxiety sensitivity may be susceptible to anxiety disorders. Our results provide a biological mechanism for this perspective in a way that the functional coupling between the LC and insula is related to AA, a core feature of pathological anxiety.

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Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.05/QQ21

Topic: G.06. Anxiety Disorders

Title: Structural insights into human brain-gut peptide cholecystokinin receptor-1

Authors: *Y. DING;
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Abstract: Cholecystokinin (CCK) receptor family belongs to class-A sevenfold transmembrane G protein-coupled receptors, and is divided into CCK1 receptor (CCK1R) and CCK2 receptor (CCK2R). CCK1R is mainly distributed in the gastro-intestinal tract, peripheral nervous system, and some regions of the brain, e.g., the area postrema, the nucleus tractus solitarius, and the hypothalamus. This paper, we reported 2 high-resolution cryo-EM structures of CCK1R signaling complexes. The structures, together with mutagenesis studies, revealed distinct features of the CCK1R ligand-binding pockets that determine CCK1R selectivity for sulfated CCK-8 and SR146131.

Disclosures: **Y. ding:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.06/QQ22

Topic: G.06. Anxiety Disorders

Support: NIH Grant GM136450
NIH Grant RL5 GM118975

Title: Examining error-related negativity as a neural marker for anxiety among college students

Authors: A. BARSEGYAN[1], **G. GUZMAN**[1], *J. SCHINDLER[2], L. APAR[1], S.-M. KANG[1];
[1]Psychology, [2]California State Univ. Northridge, Northridge, CA

Abstract: Making mistakes can induce anxiety and is inevitable throughout human nature. Accordingly, Error-Related Negativity (ERN) is an event-related potential component that appears when an individual makes erroneous responses. Previous literature suggests that ERN is a neural marker for anxiety and is measured through electrical impulses of brain wave activity. There is a notable difference between the ERN and the neural potential to correct responses, known as the Correct-Response Negativity (CRN). This response to error commission is associated with an adaptive, evolutionary mechanism that allows humans to allocate more cognitive resources for future responses. We hypothesized that students who exhibited an enhanced ERN would be associated with reporting more anxiety-related symptoms. To further elucidate on the relationship between heightened ERN amplitude and anxiety, a total of 22 college students with diverse ethnic backgrounds were asked to fill out stress and anxiety measures and then take the flanker task while their brain waves were recorded. The effects of non-interpersonal stressors such as academic performance and financial hardships were also surveyed to potentially interact with ERN. The results showed that the participants with higher ERN over CRN tended to report more achievement-related stress and panic symptoms, suggesting that this neural marker is associated with anxiety symptoms among college students.

Disclosures: **A. Barsegyan:** None. **G. Guzman:** None. **J. Schindler:** None. **L. Apar:** None. **S. Kang:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.07/Web Only

Topic: G.06. Anxiety Disorders

Title: Anxiety prevalence between nurse students of 6th grade and 8th grade

Authors: R. B. GONZÁLEZ-GARCÍA[1], M. D. VALLECILLOS BANDA[1], M. E. BARRETO-ARIAS[1], M. FERNÁNDEZ-MOYA[1], *O. JARAMILLO-MORALES[2];
[1]Univ. of Guanajuato, Irapuato, Mexico; [2]Univ. de Guanajuato, Ciudad de México, Mexico

Abstract: Anxiety levels in students are related to various factors that surround the social, emotional, family and academic environment. The objective of this article was to know the prevalence of anxiety that exists among nursing students of the last two years of the Life Sciences Division. The study was carried out in a sample of 60 students: 30 sixth-semester students and 30 eighth-semester students, to whom the STAI questionnaire was applied: Anxiety-Trait Inventory to assess transitory emotional state, and the Hamilton Scale to assess physical symptoms. Data collection was obtained through the Google Forms platform. The results reveal that eighth-semester Nursing students have high anxiety rates compared to sixth-semester students, despite the fact that they also have moderate anxiety. These results suggest that the last year of the Nursing Degree is related to higher levels of anxiety, hence it is

necessary to analyze the implementation of counseling and workshops to teach students to deal with stressful situations

Disclosures: **R.B. González-García:** None. **M.D. Vallecillos Banda:** None. **M.E. Barreto-Arias:** None. **M. Fernández-Moya:** None. **O. Jaramillo-Morales:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.08/QQ23

Topic: G.06. Anxiety Disorders

Title: Supplementation with whey peptide rich in β-lactolin improves mood states in healthy adults: A randomized, double-blind, placebo-controlled study.

Authors: *T. AYABE[1], M. SHINOHARA[2], J. SAITO[3], T. FURUYASHIKI[2], K. TOBA[4], S. UMEDA[5], Y. ANO[1];
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Abstract: Background: Mental disorders have become one of the most burdensome health concerns, and thus preventive approaches to support mood states in daily life have recently gained attention. We have previously demonstrated that whey-derived glycine-thereonine-tryptophan-tyrosine tetrapeptide, designated as β-lactolin, improves cognitive and psychiatric functions in rodents via activation of dopaminergic system. We have also performed clinical trials and found that supplementation of β-lactolin improves memory function in healthy older adults. However, the effects of β-lactolin on human mood states have not been investigated. **Objective:** The aim of this study was to evaluate the effects of β-lactolin-rich whey peptide supplementation on mood states in healthy adults in a randomized, double-blind, placebo-controlled study. **Methods:** Sixty healthy adults (aged 45 to 64) with relatively low mental health were randomly allocated to receive either whey peptide tablets (containing β-lactolin 1.6 mg/day) or placebo tablets for 6 weeks. Mood states (primary outcomes) were evaluated using self-reporting questionnaires. Health related quality of life (QOL), salivary stress markers and lipid mediators were evaluated as secondary outcomes. **Results:** Compared with placebo, supplementation of β-lactolin for 6 weeks significantly improved the changes in trait anxiety (p = 0.046) assessed by state-trait anxiety inventory and in subjective stress (p = 0.043) assessed in perceived stress scale. In QOL assessment, score changes in vitality subscale (p = 0.033) and mental health summary score (p = 0.039) in 36-Item Short-Form Health Survey were improved in β-lactolin group. The levels of salivary immunoglobulin A were significantly higher in β-lactolin group (p = 0.045). In subgroup analysis by median age (54.5 years), subjective stress and salivary prostaglandin levels were significantly decreased by β-lactolin supplementation in 45-54 years old subgroup. **Conclusions:** Supplementation of β-lactolin improves mood states such as

trait anxiety and subjective stress and psychological QOL, which may be detected by immunological stress markers assessed in salivary analysis.

Disclosures: **T. Ayabe:** A. Employment/Salary (full or part-time):; Kirin Holdings Company, Limited. **M. Shinohara:** None. **J. Saito:** None. **T. Furuyashiki:** None. **K. Toba:** None. **S. Umeda:** None. **Y. Ano:** A. Employment/Salary (full or part-time):; Kirin Holdings Company, Limited.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.09/QQ24

Topic: G.06. Anxiety Disorders

Support: Supported by a NEA grant # 127359.

Title: Music presentation alters the metabolic and physiologic profile in normal subjects and patients within the ICU

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Abstract: Listening to music can either lead to arousal or promote a state of relaxation. Yet, the acoustic, neural, and physiologic parameters and processes that facilitate these effects are not well understood. Here, we tested the hypothesis that a custom music composition can promote healing in patients recovering from liver transplant surgery within an intensive care unit (ICU) in a hospital setting. We also presented music to normal subjects (ages 20 to 50 years) to delineate patient-specific effects from the relatively well-established calming effects of music. The music presented to all consisted of custom,15-minute music sets curated and recorded by an experienced medical musician to promote well-being. Participants' musicality, motivation for music use, and anxiety levels were assessed to evaluate if and how musicality and mental state correlates with individual physiologic changes. Musicality was scored using the standardized music background questionnaire (MUSEBAQ). We obtained cortisol samples from saliva samples ~15 minutes before and after music presentation, and also captured autonomic activity by recording electrocardiography, respiration, photoplethysmography, temperature, and electrodermal activity for 5 minutes before, during, and 5 minutes after music presentation in normal subjects and patients. Results showed a significant decrease in cortisol production in normal subjects ($P < 0.05$; $n = 11$) after music presentation. Music-mediated increases in heart rate variability (HRV), calculated via triangular interpolation of NN intervals (TINN), correlated with the subject's change in cortisol production during music presentation ($n = 7$, $P = 0.0087$).

Individual changes in cortisol production over the course of music presentation were significantly correlated with self-reported use of music as a tool for cognitive regulation (n = 7, P = 0.0218). Detailed analysis in a single patient showed significant changes in multiple cardiac parameters, including HRV, similar to that of normal, healthy subjects. Multidimensional scaling of twenty-five parameters related to HRV in a patient mapped all five instances of the music presentation condition outside of the mixed cluster of baseline conditions before and after music presentation. We propose that listening to music promotes homeostasis by transiently shifting physiological parameters towards a state of recovery that may stabilize over time.

Disclosures: J. Millard: None. **A. Perelman:** None. **M.D. Hanza:** None. **A. Schulman:** None. **P. Kota:** None. **A. Patel:** None. **J. Langley:** None. **J.S. Kanwal:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.10/QQ25

Topic: G.07. Post-Traumatic Stress Disorder

Title: Effects of childhood trauma on brain multiregional transcriptomics in subjects with posttraumatic stress disorder and major depressive disorder.

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Abstract: Background. Childhood trauma (CT) is known to have long-term effects on mental health by altering the development and plasticity of the neural circuitry, which can precipitate the onset of Major Depressive Disorder (MDD) and Posttraumatic Stress Disorder (PTSD). However, the long-term effects of CT on the molecular profiles in human brains remains largely unknown. **Methods and Results per aim.** Using human postmortem brain tissue, our first aim studied the effects of CT on bulk transcriptomic profiles of subjects with MDD and/or PTSD in three stress-processing regions [dorsolateral (dl)PFC, medial (m)PFC, and central amygdala (CeA)]. We compared bulk RNA sequencing (RNAseq) data between subjects with MDD/PTSD without CT (MDD/PTSD-*CT*; n= 92 for dlPFC and 87 for mPFC and CeA) or with CT (MDD/PTSD+*CT*; n= 64 and 67, respectively) and controls (CTR) (n=77 and 74) using *limma differential expression* analyses. We obtained differentially expressed genes (DEGs) between MDD/PTSD-CT vs CTR and MDD/PTSD+CT vs CTR and compared the DEGs with *Rank-Rank Hypergeometric Overlap test*. DEGs were the least overlapping in the dlPFC (rho = 0.534) followed by CeA (rho= 0.639) and mPFC (rho= 0.738). Due to the high variability of cell types within these brain regions, our second aim explored how changes in gene expression in

excitatory (Ex) and inhibitory (In) neurons in subjects with PTSD related to our bulk findings. We *correlated* our bulk dlPFC results with single nucleus RNAseq data from Chatzinakos et. al. (AJP, in press) on the dlPFC transcriptomic profiles of subjects with PTSD (n= 11) vs CTR (n= 11). Results showed negative correlations between MDD/PTSD+CT signatures and PTSD Ex (r= 0.204; p-val= 0.0016) and In (r= 0.335; p-val= 1.620e-5) neurons, and positive correlations between MDD/PTSD-CT and these cell types (r= 0.386; p-val= 0.002 and r= 0.104; p-val= 0.123, respectively). Our last aim studied the involvement of glucocorticoid receptor (GR)-dependent pathway on CT effects in bulk tissue. We *correlated* our bulk results from dlPFC, mPFC and CeA with RNAseq data from human induced pluripotent stem cells (iPSC)-derived neurons exposed to dexamethasone (DEX, a synthetic glucocorticoid with high GR-affinity) by Chatzinakos et. al. Results showed that the dlPFC bulk MDD/PTSD+CT signature is the only negatively correlated with GR-mediated transcriptomic changes in DEX-exposed iPSC-derived neurons (r= 0.189; p-val= 0.0029). **Conclusions.** Based on these results, we concluded that exposure to CT in the context of MDD/PTSD has a specific effect, distinct from the overall disorder, in the transcriptomic profile of PFC subregions and amygdala, which is more prevalent in the dlPFC.

Disclosures: **M. Soliva Estruch:** None. **C. Chatzinakos:** None. **C. Snijders:** None. **C. Pernia:** None. **C. DiPietro:** None. **A. Iatrou:** None. **G. Kenis:** None. **B. Rutten:** None. **C.B. Nemeroff:** None. **J. Kleinman:** None. **K. Ressler:** None. **N. Daskalakis:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.11/QQ26

Topic: G.07. Post-Traumatic Stress Disorder

Support: Operation Mend

Title: Prospective memory deficits predicted by depression and PTSD severity in treatment-seeking veterans

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Abstract: Treatment-seeking veterans often present comorbidities that may contribute to the cognitive deficits they experience, including prospective memory (PM) deficits. Failures in PM contribute to everyday functional impairments and many veterans demonstrate low performance in PM tasks, making it a worthwhile target for intervention. This study investigates the predictive value of common comorbidities: depression, PTSD, and traumatic brain injury (TBI) to PM deficits. Data was collected from 66 treatment-seeking veterans prior to their participation in

UCLA Operation Mend: a two-week intensive treatment in which they will receive individual training sessions to address their cognitive deficits as well as other mental health and TBI-related treatment. This study contains data from 51 males and 12 females (3 no response/decline to answer) between the ages 25 and 63, with an average age of 43.5. Veterans completed the PM concerns questionnaire (PMCQ), Patient Health Questionnaire (PHQ-9), PTSD Checklist (PCL-5), and self-reported traumatic brain injury history. A stepwise regression procedure was conducted, in which age, depression symptomatology (PHQ-9), PTSD severity (PCL-5), and self-reported history of TBI were used to predict PM deficits, measured by scores on the PMCQ. Only depression and PTSD severity were found to predict PMCQ scores, while TBI history and age failed to significantly predict PM deficits. There was a significant positive Pearson correlation between the PM deficits and PTSD symptom severity $r(64)= .46$, $p <.001$ and a significant positive Pearson correlation between PM deficits and depression symptom severity, $r(64)= .47$, $p<.001$. As a follow up to these findings, a series of stepwise regressions were conducted to investigate which domains of symptomology in PTSD and depression are predictive for PM deficit severity. For PTSD, only the Criterion E: Arousal and Reactivity sub-score was found to be significantly predictive of PMCQ scores. Specifically, the symptoms, both within the arousal domain, of "taking too many risks or doing things to cause themselves harm" and "having difficulty concentrating" were predictive of PM deficits. For depression, only items querying fatigue and psychomotor agitation, or retardation were significantly predictive of PMCQ scores. This study demonstrates that PTSD and depression symptom severity are possible predictors of PM deficits in treatment seeking veterans and provides specific symptoms as possible targets for intervention to reduce PM deficits. This reinforces the value of an integrated, multi-disciplinary treatment approach to improve cognitive problems, in particular PM.

Disclosures: D. Staley: None. **S. Kunrath:** None. **R. Asarnow:** None. **D. Thrasher:** None. **B.J. Knowlton:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.12/QQ27

Topic: G.07. Post-Traumatic Stress Disorder

Support: Salisbury Foundation for Research and education
WFUSOM CTSI

Title: The Effect of Comorbid Substance Use and PTSD on Brain Function Post-Treatment for Substance Abuse in a Veteran Population using Magnetoencephalography (MEG)

Authors: *S. M. ODONNELL[1], J. A. ROWLAND[2], J. R. STAPLETON-KOTLOSKI[1], D. W. GODWIN[1];
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Abstract: Military veterans and service members are uniquely susceptible to a variety of mental health disorders, with post-traumatic stress disorder (PTSD) being the most prevalent. It is estimated that 11-23% of veterans will experience PTSD in a given year. Additionally, it has been observed that up to 53% exposed to combat will have a dual diagnosis of PTSD and alcohol use disorder (AUD). The effects of PTSD and SUD individually are well established; however, effects of the co-occurring condition are not understood as clearly. The present study examined brain function in individuals completing an intensive substance use treatment program. We hypothesized that co-occurring PTSD and AUD would have both unique and interactive effects on brain function.
Study participants consisted of 47 veterans undergoing substance use disorder treatment at the Salisbury VA Healthcare System (SVAHS), specifically recruited from either a resident or intensive outpatient treatment program. Participants were diagnosed with PTSD via the Clinician Administered PTSD Scale -5 (n-28). All participants were diagnosed with substance use disorder (37 with AUD). Participation in the study occurred in the two weeks following treatment. Functional connectomes were constructed using resting-state brain activity via magnetoencephalography (MEG) whole-head CTF neuromagnometer system. Linear regression determined variables responsible for the variability between outcomes. Variables in the model consisted of PTSD diagnosis, time since last drink, and number of drinks in the two weeks preceding treatment.
Preliminary results indicated several factors that were associated with various features of the connectome. Time elapsed since the last drink was associated with the number of nodes in the connectome, Average Degree of nodes, distribution of frequencies at which connections occur across the connectome, and the proportion of connections in the gamma band. Interestingly, no significant effects of PTSD on the connectome were detected. Overall, the results suggest that recent heavy use of alcohol has the most significant effect on the connectome at the end of a treatment episode.
Support: Salisbury Foundation for Research and Education and WFUSOM CTSI.IRB #: 18-015

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Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.13/QQ28

Topic: G.07. Post-Traumatic Stress Disorder

Title: Posttraumatic Stress and Whole-brain Magnetic Resonance Spectroscopy

Authors: *A. BOLARAM[1], J. B. PURCELL[1], H. E. DARK[1], D. K. GREY[1], A. J. KNIGHT[2], D. C. KNIGHT[1];
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Abstract: Posttraumatic stress disorder (PTSD) develops following exposure to a traumatic event and has a negative impact on cognitive and affective processes. Neuroimaging studies suggest the symptoms of PTSD are associated with structural and functional alterations in brain regions that support important emotional processes. H^1-Magnetic resonance spectroscopy can advance our understanding of PTSD by identifying brain metabolites that are associated with PTSD symptoms. Therefore, the present study assessed neurometabolite concentrations among participants who reported PTSD symptoms (n = 25, [23 female], Mean Age = 22.7) and healthy controls (n=20, [15 female], Mean Age = 27.55) determined by the Clinician administered PTSD scale for DSM-5 (CAPS-5). Whole brain magnetic resonance spectroscopy and high resolution T1-weighted anatomical images were collected using a 3T Siemens Prisma scanner. Whole brain magnetic resonance spectroscopic imaging was performed using a 3D-echo-planar spectroscopic imaging sequence. Neuroimaging data were processed using a fully automated pipeline, which included spatial and spectral reconstruction, field inhomogeneity and eddy current correction, tissue segmentation, registration to the Montreal Neurological Institute template, and voxel-wise spectral fitting using LC-Model followed by intensity normalization of the spectral peaks. The resulting whole-brain data included metabolite maps of N-acetylaspartate (NAA), glutamate/glutamine (Glx), total creatine (tCr), total choline (tCh), and myo-Inositol (MINO). Differences in neurometabolite concentrations were assessed between the PTSD and control groups. Results revealed greater Glx in the putamen, parahippocampal gyrus (PHG), and superior temporal gyrus in the PTSD group compared to healthy controls. Lower levels of Glx were observed in the inferior parietal lobule (IPL) and dorsolateral prefrontal cortex (PFC) in the PTSD group. Further, compared to healthy controls, the PTSD group showed elevated levels of NAA in the posterior cingulate cortex (PCC), IPL, thalamus, PHG, and dorsomedial PFC. In addition, the PTSD group showed higher levels of tCr and tCh in PCC, putamen, and insula. The PTSD group also showed higher levels of MINO in the IPL, PCC, and dorsolateral PFC than healthy controls. Lower MINO was also observed within the superior parietal lobe in the PTSD group. These results suggest that variations in neurometabolites may underlie the symptoms of PTSD.

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Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.14/RR1

Topic: G.07. Post-Traumatic Stress Disorder

Support: NIH Grant K00HD111352
NIH Grant R21HD100902

Title: Transgenerational impact of maternal early life adversity on cortical structure and epigenetic age acceleration

Authors: *L. FLEMING[1], A. PROFETTO[1], K. OHASHI[1], S. KATRINLI[2], A. SMITH[2], T. KLENGEL[1], K. J. RESSLER[1], K. LYONS-RUTH[3], M. TEICHER[1];
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Abstract: Adversity experienced early in life can produce long-lasting effects on the brain and behavior. For example, previous work shows that childhood maltreatment can lead to compromised structural integrity in sensory regions, as well as regions directly associated with threat-responses. Studies suggest these changes may be partially related to accelerated patterns of aging due to increased allostatic load. Evidence in recent years suggests that these effects have the potential to be intergenerationally transmitted between parents and offspring. However, studies of the intergenerational effects of childhood maltreatment on epigenetic aging have produced varied results, suggesting an importance for understanding the factors that drive variability in the relationship between maltreatment, age acceleration, and brain structure. Here, we investigate this relationship in a deeply-phenotyped cohort of mothers and infants at 4 months and 15 months of age. Structural MRI scans, childhood trauma history, and saliva samples were collected from (n=93) mothers with history of childhood maltreatment and their infant offspring. Individuals who had witnessed multiple episodes of interparental and sibling violence showed lower cortical thickness in inferior occipital cortex and fusiform cortex compared to controls. Epigenetic age acceleration in mothers, calculated from saliva-derived DNA methylation measurements, was significantly associated with that of their infants at 15 months of age. Additionally, we saw significant associations between epigenetic aging and post-natal depression, overall PTSD severity, and a particularly strong association with measures of abuse. These findings serve as indicators of both macroscale brain effects and microscale epigenetic effects of early life adversity. Together, these results demonstrate the long-lasting impact of childhood maltreatment on underlying biology and point toward potential intergenerational transmission of these effects.

Disclosures: L. Fleming: None. **A. Profetto:** None. **K. Ohashi:** None. **S. Katrinli:** None. **A. Smith:** None. **T. Klengel:** None. **K.J. Ressler:** None. **K. Lyons-Ruth:** None. **M. Teicher:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.15/RR2

Topic: G.07. Post-Traumatic Stress Disorder

Support: R01MH116156
UL1TR002494

Title: Topological data analysis reveals the impact of sleep, pain, and social function on persistent PTSD symptoms in veterans from the Mind Your Heart study

Authors: *A. E. INGEBRETSON[1,2], T. KIRSH[1,3], S. MA[1,3,4], E. KUMMERFELD[1,3], A. R. FERGUSON[5,6,9], T. C. NEYLAN[5,9,7], B. E. COHEN[5,9,8], J. L. NIELSON[1,3,2];
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Abstract: Introduction: Posttraumatic stress disorder (PTSD) affects up to 5% of the US population. Heterogeneity and evolution of PTSD symptoms over time requires identifying complex patterns and subtypes in large-scale clinical datasets, which can be computationally intense. Topological data analysis (TDA) is a topological and geometrical approach for reducing complex, high-dimensional data into its fundamental structure, which leads us to generate new hypotheses about what impacts persistent symptoms in chronic PTSD. **Methods**: Data were mined from the Mind Your Heart study, a longitudinal prospective cohort study of US military veterans consisting of multidomain data collected at baseline and 10 years of annual follow up (N = 746). Using a subset of data comprising measures of PTSD, depression, alcohol consumption, overall health, general physical functioning, and quality of life across all years (n=208), dimension reduction was performed using the non-linear Isomap algorithm with persistent homology. A network graph was then extracted from this low-dimensional space, forming five patient clusters. Variables collected across all 10 years were assessed for differences between selected clusters using ranked Kolmogorov-Smirnoff (KS) tests to identify features with potential clinical relevance to chronic PTSD. **Results**: From these five patient clusters we observed two clusters with high PTSD symptom severity at baseline, where one cluster had clinically significant improvement in depression and PTSD whereas the other did not at year 10 follow up. From the list of rank sorted KS results, given the known impact of poor sleep quality, pain, and social dysfunction on PTSD symptomology, we compared patients in these clusters on self-reported measures of these domains. Patients with persistent PTSD showed an interaction between sleep quality and pain which interfered with social relationships and mood at year 10. In contrast, patients with improving PTSD had a greater influence of social function across years 8 - 10 of the study while reporting greater social support resources. Following correction for multiple
comparisons, only pain interference with social relationships at year 10 and variables already used to define the TDA network differed significantly between these clusters, indicating that the impact of pain on social relationships may be an important factor in chronic PTSD. **Discussion**: In this study we show that chronic PTSD is exacerbated by sleep, pain and availability of social support; however this is more of a factor in the years preceding symptom progression, rather than earlier symptoms predicting those that occur many years later.

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Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.16/RR3

Topic: G.07. Post-Traumatic Stress Disorder

Title: Examining multimodal magnetic resonance imaging features for symptom assessment and prediction in veterans with chronic multisymptom illness

Authors: *M. MOORE[1,2], Y. ZHANG[1], P. J. BAYLEY[1,2], J. W. ASHFORD[1,2], A. J. FURST[1,2]; [1]War Related Illness and Injury Study Ctr., Veterans Affairs Palo Alto Hlth. Care Syst., Palo Alto, CA; [2]Stanford Univ. Sch. of Med., Stanford, CA

Abstract: The neural correlates of many health conditions veterans experience post-deployment, such as chronic multisymptom illness (CMI), post-traumatic stress disorder (PTSD), and traumatic brain injury (TBI), remain unclear. Multimodal brain imaging approaches allow for the possibility of investigating the neural correlates of complex, and potentially coexisting, health conditions in comprehensive ways by jointly characterizing features of the brain. Therefore, the present study examined multimodal features of structural and diffusion magnetic resonance imaging data from veterans and healthy controls (HC). Veteran data were acquired at the War Related Illness and Injury Study Center (n = 181), and HC data were acquired from a public research database (n = 122). Targeted examples of veteran-relevant health conditions, including CMI, PTSD, and TBI symptoms, were assessed based on screening information obtained from participants. Among veterans who met criteria for CMI, subgroups endorsed symptoms of PTSD, TBI, both PTSD and TBI, or neither. Multimodal data fusion was performed to integrate gray matter volume and fractional anisotropy maps. Results identified components consistent with cortical and subcortical systems in veterans and HC across imaging modalities. Anatomical patterns revealed by components indicated that veterans who endorsed symptoms showed modulated regions within distributed brain systems. Further analyses expanded on these findings using machine learning to predict health condition symptoms. Together, the present results support the idea that multimodal biomarkers of conditions such as PTSD and TBI, comorbid with CMI, can be captured and characterized to better elucidate the neural correlates of chronic health conditions in veterans.

Disclosures: **M. Moore:** None. **Y. Zhang:** None. **P.J. Bayley:** None. **J.W. Ashford:** None. **A.J. Furst:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.17/RR4

Topic: G.07. Post-Traumatic Stress Disorder

Support: NSERC RGPIN-2016-05964
Workers Compensation Board of Manitoba
University of Manitoba

Title: Investigating markers of Alzheimer's disease in posttraumatic stress disorder using an automated learning algorithm and magnetic resonance imaging

Authors: *G. YAKEMOW[1,5], T. KOLESAR[1,5], I. BEHESHTI[1,5], N. WRIGHT[1,5], L. RYNER[2], S. CHAULK[3], R. PATEL[3], J. KO[1,5,4];
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Abstract: Posttraumatic stress disorder (PTSD) is a mental health disorder caused by experiencing or witnessing traumatic events. PTSD symptoms include intrusive memories, avoidant behaviors, anxiety, flashbacks and negative changes in mood and cognition. Symptom severity is measured using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Recent studies show that patients with PTSD have an increased risk of developing Alzheimer's disease (AD), but there is currently no way to predict which patients will go on to develop AD. We previously developed a machine learning-based AD designation (MAD) algorithm to objectively distinguish neural activity between AD patients and healthy controls (HC) using neuroimaging modalities.[1] The objective of this study is to identify brain anatomical and activity markers in PTSD that may relate to potential increased risk of developing AD. 67 participants were recruited from a clinical trial performed by our lab for treatment-seeking PTSD individuals and age-matched HC (PTSD: n = 40; 14M:26F; age = 40.0 ± 3.6; HC: n = 27; 11M:16F; age = 35.4 ± 5.2). We calculated MAD scores for each participant using pseudo-continuous arterial spin labeling (pCASL) data. We assessed grey matter (GM) volume using voxel-based morphometry of structural MRI data. Correlations between MAD scores, CAPS-5 scores, and GM volume were assessed using SPSS. A significant reduction of GM in the temporal lobe was observed in the PTSD group compared to HC (pFWE= 0.006). Additionally, MAD scores significantly correlated with CAPS-5 scores in the PTSD group (Pearson's r = 0.363, p = 0.021). GM volume inversely correlated with CAPS-5 scores in the PTSD group (Pearson's r = -0.428, p = 0.006). PTSD participants who demonstrated increased symptom severity correlated with increased GM atrophy and increased AD-like brain activity. PTSD patients demonstrated significant GM atrophy in the medial temporal lobe, one of the earliest markers for AD progression.[2] These results show promising potential for early diagnosis of AD in an at-risk population, in the hopes for allowing for an early treatment method. 1. Katako, A. et al. (2018). PMID:30185806; 2. De Flores et al. (2022).PMID:35086906

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Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.18/RR5

Topic: G.07. Post-Traumatic Stress Disorder

Title: White matter microstructure in posttraumatic stress disorder

Authors: *C. A. SANDERS[1], A. BOLARAM[1], D. K. GREY[1], H. E. DARK[1], J. B. PURCELL[1], A. J. KNIGHT[2], D. C. KNIGHT[1];
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Abstract: Posttraumatic Stress Disorder (PTSD) is associated with the dysfunction of emotion expression and regulation processes. These emotional processes are associated with a neural network that includes the prefrontal cortex, inferior parietal lobule, hippocampus, amygdala, and hypothalamus. These brain regions are connected by white matter tracts that include the superior longitudinal fasciculus, cingulum bundle, uncinate fasciculus, and stria terminalis/fornix. Therefore, determining the relationship between posttraumatic stress and the microstructure of these white matter tracts may offer new insight into the neurobiological processes that underlie PTSD. The present confirmatory study examined the relationship between white matter microstructure and posttraumatic stress. Forty five participants (PTSD = 15; Controls = 30; M_{age} = 26.7 years; SD = 11.8) were recruited for this study. Participants completed the Life Events Checklist and Clinician-Administered PTSD Scale for DSM-5. Diffusion-weighted magnetic resonance imaging (TR = 3230 ms, TE = 89.2 ms, FOV = 210 mm^2, matrix size = 140 x 140, 1.5 mm isotropic resolution) was acquired in 98 directions (b = 0, 3000 s/mm^2). Voxel-wise cross-subject analysis of white matter fractional anisotropy (FA) data was completed using Tract-Based Spatial Statistics. We hypothesized that FA would be greater within the stria terminalis/fornix, but lower in the superior longitudinal fasciculus, cingulum bundle, and uncinate fasciculus in participants with PTSD compared to healthy controls. We also hypothesized that FA would vary with PTSD symptom severity (positively: stria terminalis/fornix; negatively: superior longitudinal fasciculus, cingulum bundle, and uncinate fasciculus). Results showed greater FA in the uncinate fasciculus and stria terminalis/fornix in participants with PTSD compared to healthy controls. In addition, PTSD symptom severity was positively related to stria terminalis/fornix FA and negatively related to cingulum bundle FA. These results suggest that differences in the white matter of the cingulum bundle, uncinate fasciculus, and stria terminalis/fornix may underlie symptom expression in PTSD.

Disclosures: C.A. Sanders: None. **A. Bolaram:** None. **D.K. Grey:** None. **H.E. Dark:** None. **J.B. Purcell:** None. **A.J. Knight:** None. **D.C. Knight:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.19/RR6

Topic: G.07. Post-Traumatic Stress Disorder

Support: MOMRP

Title: Predicting resiliency and vulnerability factors of post-traumatic stress disorder using long term mirna changes in a large military cohort - millennium cohort study

Authors: *N. GARY[1,2], A. LAWRENCE[1,3], R. YANG[1], A. GAUTAM[1], C. J. DONOHO[4], T. M. POWELL[4], A. HOKE[1], G. DIMITROV[1], M. JETT[1], R. HAMMAMIEH[1];
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Abstract: Post-traumatic stress disorder (PTSD) can be a debilitating disorder associated with considerable morbidity; therefore, it is critical to determine resiliency and vulnerability factors for long-term outcomes associated with PTSD including comorbidities (depression, substance abuse, pain syndromes) as well as functional health status. The purpose of this study is to discover microRNA (miRNA) signatures corresponding to different trajectories of PTSD symptoms and associated comorbidities. This study investigates whether the use of miRNA profiles can have a predictive effect on the changes in symptom severity (i.e., physical, social, emotional functioning) across individuals, as well as also differentiating between individuals who screen positive for PTSD versus those who do not. The Millennium Cohort Study is a large military prospective study conducted since 2001, with the goal of assessing the health of military personnel. 352 participants were screened for PTSD using the PTSD CheckList - Civilian Version (PCL-C). Blood samples (N = 1036) were collected and assayed for miRNA profiles using next-generation sequencing (NGS) techniques. Four differential analyses were conducted to compare post-deployment PTSD and healthy controls using pre-deployment samples between those who developed PTSD after deployment and those did not, and to identify the miRNA profiles associated with the PTSD symptom changes. Our data showed that certain miRNA changed over time in response to the physical and psychological stressors during the deployment of active-duty personnel. Data shows a significant dysregulation of miRNA genes involved in the stress response, inflammation, and oxidative stress were observed between post-deployment PTSD and control groups. The two miRNA that distinguished the groups the most before deployment were hsa-miR-9-5p and has-miR-127-3p. In addition, using PCL-C score, six miRNAs correlated with the changes of measured PTSD severity. Our findings help provide important insights into the impact that psychological and physical stressors experienced by active-duty personnel have on the molecular changes that occur at the miRNA level. These data may be used to inform the development of new therapeutic interventions to prevent or mitigate the effects of these stressors on the health and well-being of military personnel. To confirm and extend these findings, and to examine the resiliency and vulnerability factors for long-term outcomes associated with PTSD including comorbidities, further studies will be required.

Disclosures: N. Gary: None. **A. Lawrence:** None. **R. Yang:** None. **A. Gautam:** None. **C.J. Donoho:** None. **T.M. Powell:** None. **A. Hoke:** None. **G. Dimitrov:** None. **M. Jett:** None. **R. Hammamieh:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.20/RR7

Topic: G.07. Post-Traumatic Stress Disorder

Support: NIH DA018343

Title: A Proteome-wide, Multi-Omics Analysis Implicates Novel Protein Dysregulation in Post-Traumatic Stress Disorder

Authors: *J. WANG[1], H. LI[2], R. WILSON[3], W. WANG[4], T. T. LAM[3,4], D. A. LEWIS[5], J. R. GLAUSIER[5], P. E. HOLTZHEIMER[6,7], M. J. FRIEDMAN[6,7], K. WILLIAMS[3,4], M. PICCIOTTO[1], A. C. NAIRN[1,3], J. H. KRYSTAL[1,7], R. S. DUMAN[1,7], H. ZHAO[2], M. J. GIRGENTI[1,7];
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Abstract: Post-traumatic stress disorder (PTSD) is a common and disabling psychiatric disorder. Here we present findings from the first proteome-wide study of the postmortem PTSD brain. We performed tandem mass spectrometry on large cohort of donors (N = 66) in two prefrontal cortical areas and found differentially expressed proteins and co-expression modules disturbed in PTSD. Integrative analysis pointed to hsa-mir-589 as a regulatory miRNA responsible for disruptions in neuronal protein networks for PTSD, including the GABA vesicular transporter, SLC32A1. In addition, we identified significant enrichment of risk genes for Alzheimers Disease, major depression, and schizophrenia within PTSD co-expression protein modules, suggesting shared molecular pathology. Our findings highlight the altered proteomic landscape of postmortem PTSD brain and provide a novel framework for future studies integrating proteomic profiling with transcriptomics in postmortem human brain tissue.

Disclosures: J. Wang: None. **H. Li:** None. **R. Wilson:** None. **W. Wang:** None. **T.T. Lam:** None. **D.A. Lewis:** None. **J.R. Glausier:** None. **P.E. Holtzheimer:** None. **M.J. Friedman:** None. **K. Williams:** None. **M. Picciotto:** None. **A.C. Nairn:** None. **J.H. Krystal:** None. **R.S. Duman:** None. **H. Zhao:** None. **M.J. Girgenti:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.21/RR8

Topic: G.07. Post-Traumatic Stress Disorder

Support: National PTSD Brain Bank intramural research program

Title: Transcriptomic alterations across human hippocampal subfields in posttraumatic stress disorder

Authors: *T. P. NGUYEN[1], J. WANG[1], D. A. CRUZ[2], D. A. LEWIS[3], P. E. HOLTZHEIMER[4], J. H. KRYSTAL[1], D. E. WILLIAMSON[2], M. J. GIRGENTI[1];
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Abstract: Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder occurring in the aftermath of a highly traumatizing event. The hippocampus is a key component in the "fear" circuitry of the brain, and previous studies have implicated structural and molecular dysfunction in PTSD patients. PTSD is highly comorbid with major depressive disorder (MDD), and the two disorders share genetic, molecular and neurobiological alterations in the frontal cortex and subcortical regions of the brain. Previous work from our lab has identified changes in DNA methylation in the PTSD hippocampus, suggesting epigenetic changes after psychological trauma that may affect gene expression. We therefore endeavored to identify gene expression patterns within the PTSD and MDD hipppocampus. We performed bulk-tissue RNA-sequencing on three hippocampal subfields (dentate gyrus, CA, and subiculum) dissected from postmortem brains of 132 donors (49 PTSD, 43 MDD, 40 non-psychiatric controls). Our analysis reveals distinctive patterns of differential expression and splicing between PTSD and controls. Transcript co-expression analysis identifies hub genes and novel candidates specific to each subregion. Our findings highlight the regional diversity of brain gene expression and provide insights into the molecular mechanisms underlying PTSD and hippocampal function.

Disclosures: T.P. Nguyen: None. **J. Wang:** None. **D.A. Cruz:** None. **D.A. Lewis:** None. **P.E. Holtzheimer:** None. **J.H. Krystal:** None. **D.E. Williamson:** None. **M.J. Girgenti:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.22/RR9

Topic: G.07. Post-Traumatic Stress Disorder

Title: Single cell genomic analysis reveals cell type-specific molecular signatures in the human PTSD prefrontal cortex

Authors: *A. HWANG[1], M. SKARICA[3], C. LEE[2], J. WANG[4], H. LI[6], S. XU[2], T. STUDY GROUP[5], D. A. CRUZ[7], D. WILLIAMSON[8], H. ZHAO[6], N. SESTAN[3], J. KRYSTAL[4,9], K. A. YOUNG[10,11], J. ZHANG[2], M. GIRGENTI[4,9];
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Sci., Duke Univ., Durham, NC; [8]Dept. of Psychiatry and Behavioral Sci., Duke Sch. of Med., Durham, NC; [9]US Dept. of Veterans Affairs, Natl. Ctr. for PTSD, New Haven, CT; [10]Dept. of Psychiatry, Texas A&M Col. of Med., Bryan, TX; [11]Central Texas Veterans Hlth. Care Syst., Temple, TX

Abstract: Post-traumatic stress disorder is a multigenic disorder occurring in the aftermath of severe trauma exposure. Recent studies have begun to detail the molecular biology of the postmortem PTSD brain using bulk-tissue transcriptomic and epigenetic analyses. However, given the array of PTSD-perturbed molecular pathways identified thus far, it is unlikely that a single cell type is responsible. It is therefore necessary to uncover the individual cell types contributing to the molecular pathology of PTSD. We isolated ~1M nuclei from human postmortem dorsolateral prefrontal cortex from cases and controls for single nucleus RNA sequencing (snRNA-seq) across three diagnostic cohorts: PTSD, MDD (Psychiatric control), and neurotypical controls to identify neuronal and non-neuronal cell type clusters and cell type-specific gene expression changes. We tested whether differentially expressed genes and their pathways are enriched for specific biological functions in each cell population. We then performed single cell ATAC-sequencing on nuclei from the same donors as our snRNA-seq, to measure chromatin assembly dynamics in PTSD. We also test whether genome-wide significant SNPs identified from the MVP GWAS of PTSD are associated with gene expression within specific cell types of the DLPFC and whether open chromatin regions were enriched for PTSD risk variants. From 14 distinct cell type clusters we identified over 1100 FDR significant differentially expressed genes and confirmed expression changes of several genes implicated in PTSD pathophysiology by FISH. We found PTSD specific cis-regulatory elements for several genes including *ELFN1*, *MAD1L1*, *CRHR1* and *UBA7*. Integration of large GWAS data from MVP with our snATAC dataset showed enrichment of variants for PTSD and its quantitative clinical traits (hyperarousal, re-experiencing and avoidance) within excitatory and inhibitory neurons. Taken together, this work is the first step in the creation of a cell type-specific atlas of stress disorders. Annotating the postmortem brain genome to characterize risk alleles within specific cell types will help determine which biological processes are most impacted by stress. These findings provide a global picture of the cell type-specific molecular regulatory mechanisms that govern stress effects on the human prefrontal cortex and provides a blueprint for integrating single cell type genomic data to characterize the molecular landscape of other brain regions implicated in traumatic stress.

Disclosures: A. Hwang: None. **M. Skarica:** None. **C. Lee:** None. **J. Wang:** None. **H. Li:** None. **S. Xu:** None. **T. Study Group:** None. **D.A. Cruz:** None. **D. Williamson:** None. **H. Zhao:** None. **N. Sestan:** None. **J. Krystal:** None. **K.A. Young:** None. **J. Zhang:** None. **M. Girgenti:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.23/RR10

Topic: G.07. Post-Traumatic Stress Disorder

Support: National Center for PTSD Investigator Award

Title: An integrated genomics analysis of PTSD across brain regions and cell types

Authors: *V. K. MARTINEZ[1], H. LI[3], A. HWANG[4], D. A. CRUZ[5], D. WILLIAMSON[6], J. ZHANG[4], H. ZHAO[3], J. H. KRYSTAL[7], M. J. GIRGENTI[2];
[1]Psychiatry, [2]Yale Univ. Sch. of Med., New Haven, CT; [3]Yale Univ., New Haven, CT; [4]USC, Irvine, CA; [5]Psychiatry & Behavioral Sci., Duke Univ., Durham, NC; [6]Duke Univ. Med. Ctr., Durham, NC; [7]West Haven VA Med. Ctr., West Haven, CT

Abstract: Gene regulation is dynamic and cell type specific. Differences in regulation at various levels (genetic, epigenomic, and transcriptomic) contribute to psychiatric disorders, such as PTSD, by converging on specific biological pathways that have clinical significance. Understanding the neurobiology and molecular mechanisms associated with PTSD will require investigation of gene regulation at multiple levels across multiple brain regions. We generated a multi-omic, postmortem brain dataset comparing PTSD, neurotypical control, and a psychiatric control (major depressive disorder), that includes RNA expression and DNA methylation from the dorsolateral prefrontal cortex, amygdala and the hippocampus. Single nucleus RNA-seq data was generated at cell type-specific resolution with matching bulk-tissue RNA-sequencing for the dorsolateral prefrontal cortex. Targeted methyl-sequencing was performed on the same cohort for the amygdala and hippocampal subregions. We identified differentially enriched pathways in PTSD and MDD that included glucocorticoid signaling, GABA transmission, and inflammation. PTSD risk loci, including *CRHR1*, *ELFN1*, and *MAD1L1*, had differential expression at the RNA and methylation level. PTSD and MDD have unique genomic characteristics and this approach demonstrates how convergent pathways across molecular modalities contribute to stress-associated etiology.

Disclosures: V.K. Martinez: None. **H. Li:** None. **A. Hwang:** None. **D.A. Cruz:** None. **D. Williamson:** None. **J. Zhang:** None. **H. Zhao:** None. **J.H. Krystal:** None. **M.J. Girgenti:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.24/Web Only

Topic: H.05. Working Memory

Support: 1K01MH121777-01

Title: Effect of repetitive transcranial magnetic stimulation on anxiety

Authors: *M. TEFERI[1], M. PATEL[2], A. CASALVERA[1], W. MAKHOUL[1], D. OATHES[1], Y. I. SHELINE[1], N. L. BALDERSTON[3];
[1]Univ. of Pennsylvania, Philadelphia, PA; [3]Univ. of Pennsylvania, [2]Univ. of Pennsylvania Deptartment of Psychiatry, Philadelphia, PA

Abstract: BACKGROUND: Repetitive transcranial magnetic stimulation (rTMS) treatment protocols have been effective in reducing anxiety symptoms comorbid with depression but have not shown the same efficacy in non-depressed individuals, calling for a novel approach to general anxiety reduction. In this study, intermittent theta burst stimulation (iTBS) will be used to stimulate the right dorsolateral prefrontal cortex (dlPFC) to target regions in the fear/anxiety circuit.
OBJECTIVE: Our aim is to determine the effects of a one-week course of iTBS on anxiety and anxiety-related working memory deficits in comparison to the sham stimulation. METHOD: In this double-blinded, cross-over design, 28 healthy subjects underwent 12 study visits over a 4-week period. They received 4 iTBS sessions, which included ten 60-pulse iTBS trains, over the course of a week with a post-stimulation testing session occurring 24 hours following the final iTBS session. The order of active/sham delivery was counterbalanced across subjects. The effects of the stimulation on anxiety and anxiety-related working memory deficits were assessed using the unpredictable shock-threat paradigm and Sternberg working memory task during threat of shock, respectively. The unpredictable shock-threat task consists of three conditions: neutral or no shock, predictable shock in presence of a cue, or unpredictable shock. In the Sternberg working memory task, letters are shown individually in which subjects have to memorize them in the order presented (maintain) or alphabetically (sort) and respond if a letter and its position in the series is correct or not correct.
RESULTS: Results show that there was a significant main effect in startle responses for both coil and response types. Both fear potentiated startle (FPS) and anxiety potentiated startle (APS) increased after active compared to sham iTBS. Consistent with previous studies, FPS responses were greater than APS responses. For sternberg accuracy and reaction time, there were no main effects of either coils or conditions.
CONCLUSION: Contrary to our hypothesis, these findings suggest that iTBS to the right dorsolateral prefrontal cortex increased anxiety compared to sham stimulation. Future studies can examine the effects of iTBS in anxious patients.
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Disclosures: M. Teferi: None. **M. Patel:** None. **A. Casalvera:** None. **W. Makhoul:** None. **D. Oathes:** None. **Y.I. Sheline:** None. **N.L. Balderston:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.25/RR11

Topic: H.05. Working Memory

Support: K01 Award K01MH121777

Title: Interleaved TMS/fMRI shows that threat decreases dlPFC-mediated top-down regulation of emotion processing.

Authors: *M. PATEL, M. TEFERI, A. CASALVERA, K. LYNCH, W. MAKHOUL, D. OATHES, Y. SHELINE, N. BALDERSTON;
Univ. of Pennsylvania Dept. of Psychiatry, Philadelphia, PA

Abstract: Background: The right dorsolateral prefrontal cortex (dlPFC) has been indicated to be a key region in the cognitive regulation of emotion by many previous neuromodulation and neuroimaging studies. However, there is little direct causal evidence supporting this top-down regulation hypothesis. Furthermore, it is unclear whether contextual threat impacts this top-down regulation. By combining TMS/fMRI, this study aimed to uncover the impact of unpredictable threat on TMS-evoked BOLD response in dlPFC-regulated emotional networks. Based on the previous findings linking the dlPFC to the down-regulation of emotional network activity, we hypothesized TMS pulses would deactivate activity in anxiety expression regions, and that threat would reduce this top-down regulation.
Methods: 44 healthy controls (no current or history of psychiatric disorders) were recruited to take part in a broader study. Subjects completed the neutral, predictable, and unpredictable (NPU) threat task while receiving TMS pulses to either the right dlPFC or a control region. dlPFC targeting was based on data from a separate targeting session, where subjects completed the Sternberg working memory (WM) task inside the MRI scanner.
Results: When compared to safe conditions, subjects reported significantly higher levels of anxiety under threat conditions. Additionally, TMS-evoked responses in the left insula (LI), right sensory/motor cortex (RSM), and a region encompassing the bilateral SMA regions (BSMA) differed significantly between safe and threat conditions. There was a significant TMS-evoked deactivation in safe periods that was significantly attenuated in threat periods across all 3 regions.
Conclusions: These findings suggest that threat decreases dlPFC-regulated emotional processing by attenuating the top-down control of emotion, like the left insula. Critically, these findings provide support for the use of right dlPFC stimulation as a potential intervention in anxiety disorders.

Disclosures: M. Patel: None. **M. Teferi:** None. **A. Casalvera:** None. **K. Lynch:** None. **W. Makhoul:** None. **D. Oathes:** None. **Y. Sheline:** None. **N. Balderston:** None.

Poster

PSTR295. Human Studies and Therapeutic Approaches for Anxiety and PTSD

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.26/RR12

Topic: H.05. Working Memory

Support: K01MH121777

Title: Threat of shock increases distractor susceptibility during the short-term maintenance of visual information.

Authors: *A. M. CASALVERA[1], M. GOODWIN[3], K. LYNCH[2], M. TEFERI[1], M. PATEL[1], C. GRILLON[3], M. ERNST[3], N. L. BALDERSTON[1];
[1]Psychiatry, Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of Pennsylvania, Philadelpha, PA; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: BACKGROUND: Work on anxiety related attention control deficits suggests that elevated arousal impacts the ability to filter out distractors. To test this, we designed a task to look at distractor suppression during periods of threat. We administered trials of a visual short-term memory (VSTM) task, during periods of unpredictable threat, and hypothesized that threat would impair performance during trials where subjects were required to filter out large numbers of distractors.
METHOD: Experiment 1 involved fifteen healthy participants who completed one study visit. They performed four runs of a VSTM task comprising 32 trials each. Participants were presented with an arrow indicating left or right, followed by an array of squares. They were instructed to remember the target side and disregard the distractors on the off-target side. A subsequent target square was shown, and participants indicated whether it matched one of the previously presented target squares. The trial conditions included 50% matches and 50% mismatches, with an equal distribution of left and right targets. The number of target and distractor squares varied systematically, with high (4 squares) and low (2 squares) target and distractor conditions. Trials alternated between periods of safety and threat, with startle responses recorded using electromyography (EMG) following white noise presentations. Experiment 2 involved twenty-seven healthy participants who completed the same VSTM task inside an MRI scanner during a single study visit. The procedure mirrored that of Experiment 1, except for the absence of white noise presentations.
RESULTS: For Experiment 1, subjects showed significantly larger startle responses during threat compared to safe period, supporting the validity of the threat manipulation. However, results suggested that the white noise probes interfered with performance. For Experiment 2, we found that both accuracy was affected by threat, such that distractor load negatively impacted accuracy only in the threat condition.
CONCLUSION: Overall, these findings suggest that threat affects distractor susceptibility during the short-term maintenance of visual information. The presence of threat makes it more difficult to filter out distracting information. We believe that this is related to hyperarousal of parietal cortex, which has been observed during unpredictable threat.

Disclosures: A.M. Casalvera: None. **M. Goodwin:** None. **K. Lynch:** None. **M. Teferi:** None. **M. Patel:** None. **C. Grillon:** None. **M. Ernst:** None. **N.L. Balderston:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.01/RR13

Topic: G.09. Drugs of Abuse and Addiction

Support: DNAA (NIAAA): T32 AA 025606
DEARC: P50 AA017823/S1
NADIA: U01AA028710

Title: Sex dependent effects of delayed exercise in transgenic rat model of Alzheimer's Disease (TgF344-AD) following adolescent binge-like ethanol consumption

Authors: N. REITZ[1], ***P. NUNES**[2], L. M. SAVAGE[3];
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Abstract: There is growing evidence that alcohol-related brain damage (ARBD) during a critical developmental timepoint, such as adolescence, interacts with AD-related pathologies to accelerate disease progression later in life. Furthermore, female humans and rodents, show more rapid cognitive decline and accelerated progression of brain atrophy. The current study investigates whether delayed voluntary exercise in mid-adulthood can recover memory deficits caused by the interactions between ethanol exposure in adolescence and AD-transgenes. To study this, the current project utilized a transgenic rat model of AD (TgF344-AD) and an adolescent intermittent ethanol (AIE) exposure model of binge drinking. Male and female TgF344-AD and wildtype F344 rats (WT) were exposed to an intragastric gavage of water (control) or 5g/kg of 20% ethanol (AIE) for a 2 day on/off schedule throughout adolescence (PD27-57). At 6 months old, rats either remained in their home cage (control) or were placed in a voluntary wheel running apparatus for 4 weeks. At 7 months old, all rats were tested on spatial working memory and pattern separation. Voluntary wheel running recovers spatial working memory deficits assessed by spontaneous alternation selectively in female rats with TgF344-AD exposed to AIE. Voluntary exercise also recovers the pattern separation impairment in control TgF344-AD female rats, but provided only a trend towards improvement for AIE-exposed TgF344-AD female rats. This delayed exercise had no effect on behavior in male rats. There were also sex-dependent effects on brain pathology: Exercise improves the integration of recently born neurons in AIE-exposed TgF344-AD female rats. In contrast, in only male AIE-exposed TgF344-AD, exercise decreases amyloid burden in both the hippocampus and entorhinal cortex. The number of neurons expressing the cholinergic phenotype was not affected by AD transgenes in either sex. AIE, selectively in females, reduced cell counts of the cholinergic phenotype. Unexpectedly, exercise suppressed cholinergic cell counts in both male and female rats. Our data provide support that even after symptom onset, AIE and AD-related cognitive decline, along with the corresponding neuropathologies, can be rescued with exercise in unique sex-specific ways.

Disclosures: **N. Reitz:** None. **P. Nunes:** None. **L.M. Savage:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.02/RR14

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH grant 5U01AA028710-03
NIH grant 5P50AA017823-14 5327

Title: Voluntary wheel running exercise rescues cortical acetylcholine efflux during spontaneous alternation in female rats and novel object in place behavior in male rats following adolescent intermittent ethanol exposure

Authors: *M. J. FECIK, P. T. NUNES, L. M. SAVAGE;
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Abstract: Adolescent intermittent ethanol (AIE) exposure has been shown to cause significant reductions in cholinergic phenotype throughout the basal forebrain, which persists into adulthood. Cortical acetylcholine (ACh) efflux from projections originating in basal forebrain structures have been shown to be blunted by AIE, both in the medial prefrontal cortex (mPFC) and orbitofrontal cortex during spontaneous alternation maze exploration. While this is likely due to a reduction in markers of cholinergic phenotype throughout the basal forebrain, it is unlikely that cholinergic cells are dying off, as it has been shown that voluntary wheel running exercise (VEx), can prevent AIE-induced loss of choline acetyltransferase if used during treatment and reverse the loss if used after treatment. Therefore, the goal of the current study was to investigate whether VEx following AIE treatment could rescue ACh efflux in the mPFC during spontaneous alternation. 62 Long Evans rats of both sexes were given either AIE treatment via intragastric gavage of 20% ethanol (5mg/kg) or tap water on a two-day-on two-day-off schedule from postnatal day 25 to 54. Following AIE, all rats were given surgery to implant a guide cannula into the mPFC. Afterwards, AIE and control rats were assigned to either a cage with a running wheel attached from P75 to 105 (VEx), or to remain in their home cage during that time (Stat). Rats had free access to the wheels and running data was recorded via an infrared beam breaker. Following VEx, rats were run on a four-arm spontaneous alternation maze, during which a probe was inserted into the guide cannula to collect extracellular ACh efflux. We found that mPFC ACh efflux was blunted following AIE exclusively in females, a consequence that was rescued by VEx. In males, AIE did not blunt ACh efflux, but there was a trend toward an increase in efflux in VEx rats regardless of AIE treatment. Following this experiment, we investigated a cholinergic dependent behavior, the Novel object in place (NOP) task. 32 Sprague Dawley rats of both sexes were put through the same AIE and VEx paradigm as described above. Following this, subjects were run on NOP, in which they spent two days habituating to the objects, one of which was relocated on the third day. The time spent investigating the moved object and the unmoved object was recorded. We found that male AIE rats showed a preference for the unmoved object, which was rescued via VEx. There were no effects of AIE or VEx in female rats. Overall, these results show that there may be sex difference in cholinergic dependent behaviors and neurochemistry following AIE, which may be rescued with voluntary wheel running exercise.

Disclosures: **M.J. Fecik:** None. **P.T. Nunes:** None. **L.M. Savage:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.03/RR15

Topic: G.09. Drugs of Abuse and Addiction

Support: DEARC: P50AA017823
NADIA: U01AA028710

Title: Modulating the p75NTR during adolescent intermittent ethanol exposure preserves basal forebrain cholinergic phenotype, prefrontal cortical acetylcholine signaling, and sustained attention performance

Authors: *B. T. KIPP, L. M. SAVAGE;
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Abstract: Adolescent intermittent ethanol exposure (AIE) recapitulates the binge withdrawal ethanol consummatory patterns of adolescents and facilitates long-lasting changes in neurobehavioral functioning across the lifespan. Basal forebrain cholinergic neurons are particularly susceptible to the toxic effects of AIE, leading to loss of the expression of the cholinergic phenotype, reductions in prefrontal cortical ACh release, and impairments across several cognitive domains. While the presence of dysregulated target-derived pro and mature neurotrophins during AIE suggests a potential causative role in AIE-associated cholinergic degeneration, this mechanism has mostly been unexplored. There is a dichotomous relationship between mature neurotrophins (NGF and BDNF), which are crucial for the development and maintenance of cholinergic neurons through binding and retrograde transport through TrkA and TrkB receptors, and proneurotrophins (proNGF and proBDNF), which can exert degeneration through p75NTR. This system has recently been explored as a therapeutic target in multiple neuropathologies- including alcohol use disorder. We sought to further understand the mechanism of cholinergic degeneration in AIE by manipulating the p75NTR during AIE with the use of LM11A-31, a p75NTR modulator, and examined the cholinergic profile and associated cholinergic and cognitive function in adulthood. Male and female Sprague Dawley rats were administered 5g/kg of 20% ethanol via intragastric gavage from PND 25-57 following a two-day-on-two-day off schedule. A subset of rats was also administered 50mg/kg LM11A-31 twice a day, 30 minutes before and 8 hours following each ethanol gavage. In adulthood, rats were tested on a sustained attention task, revealing attention deficits in AIE-treated animals, but not animals co-treated with LM11A-31 or controls. Additionally, reductions in prefrontal cortical ACh activity were detected in AIE rats on this task during cue presentation and reward through fiber photometry with the GRAB ACh 3.0 biosensor. Moreover, AIE-treated rats were also found to have significant reductions in the cortical projection Nucleus Basalis Magnocellularis cholinergic cell population alongside reductions in TrkA receptor co-expression. LM11A-31 treatment during adolescence was found to have protective effects on cholinergic cell populations and TrkA receptor co-expression in AIE-treated animals, but not animals that did not

receive AIE. Taken together these findings highlight a causative role of pro neurotrophin-p75NTR dysregulation in cholinergic degeneration in AIE.

Disclosures: B.T. Kipp: None. **L.M. Savage:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.04/RR16

Topic: G.09. Drugs of Abuse and Addiction

Support: U01 AA019972

Title: Social Dominance and Social Behavior: Sex-Specific Impact of Adolescent Intermittent Ethanol Exposure

Authors: *D. T. APPLEGATE[1], E. I. VARLINSKAYA[1], D. F. WERNER[2];
[1]Psychology, [2]Psychology and Behavioral Neurosci., Binghamton Univ., Binghamton, NY

Abstract: Adolescent alcohol use is a significant public health concern, with binge drinking during adolescence associated with adverse health outcomes, including an increased risk of developing alcohol use disorder as well as affective disorders. Preclinical models of adolescent binge drinking, particularly adolescent intermittent ethanol (AIE) exposure models have been used for assessment of long-lasting behavioral alterations associated with adolescent alcohol use. While previous research from our lab has shown that males are particularly sensitive to AIE effects on social behavior, exhibiting increased social anxiety-like behavior in adulthood, it is not known whether AIE can affect social dominance in a sex-dependent manner. This study was designed to (a) investigate the impact of AIE exposure on social status and (b) determine whether dominant or subordinate-like adolescent or adult social status predict social behavior in adulthood. Male and female cFos-LacZ transgenic Sprague-Dawley rats were initially assessed at postnatal day (P)27 for social rank (dominant or subordinate) using the social dominance tube test (SDTT). Animals were exposed to either water (controls) or ethanol (4 g/kg, 25% solution, v/v) given intragastrically on a 2-day on, 2-day off schedule during adolescence (P28 - P53). Following a 17-day period of forced, protracted abstinence, experimental subjects were retested on the SDTT at P70. On P75, social behavior of experimental subjects was assessed in the modified social interaction test, followed by rapid brain extractions and further tissue processing. 70% of water-exposed control males changed their adolescent social status in adulthood, while only 45% of AIE-exposed males displayed changes in dominant and subordinate-like phenotypes. In females, 37.5% of water-exposed controls changed their adolescent social status in adulthood, while 45% of AIE-exposed females displayed changes in dominant and subordinate-like phenotypes. Similar to previous findings in our lab, only AIE-exposed males displayed decreased social investigation relative to water-exposed counterparts. Social status in adolescence or in adulthood did not predict (a) AIE-associated changes in social investigation in

males and females or (b) social investigation of water-exposed subjects. Future studies will assess potential changes in stress and steroid hormones (corticosterone, progesterone, testosterone) which may contribute to social status in males or females and/or social deficits observed in males following AIE.

Disclosures: D.T. Applegate: None. **E.I. Varlinskaya:** None. **D.F. Werner:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

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Program #/Poster #: PSTR296.05/RR17

Topic: G.09. Drugs of Abuse and Addiction

Support: NIAAA Grant U01 AA019925-11

Title: Adolescent intermittent ethanol-induced effects on activity, anxiety, memory & biological markers: sex-specificity and prevention by dietary choline

Authors: *K. HEALEY[1], A. BELL[1], S. MARSHALL[2], H. SWARTZWELDER[1];
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Abstract: Alcohol exposure during adolescence causes CNS and behavioral changes that persist into adulthood, particularly in the domains of memory and anxiety-related behaviors. Adolescent intermittent ethanol (AIE) exposure alters neurochemical signaling and molecular mechanisms in the brain, including disruption of the cholinergic system, which may underlie known AIE-induced behavioral deficits in adulthood. Choline is an essential nutrient and a precursor to acetylcholine, which is known to regulate attention, learning, motivation, and memory. Choline supplementation has been shown to ameliorate neurobehavioral deficits associated with prenatal ethanol exposure, and therefore may ameliorate or prevent some of the persistent behavioral effects of AIE. Adolescent male and female Sprague-Dawley (PD 29) rats were exposed to 14 doses of ethanol (5 g/kg; *intragastric gavage;* AIE) or isovolumetric water over 23 days. Daily choline (100 mg/kg, fed in 6% sweetened condensed milk) or vehicle (6% sweetened condensed milk) began on PD 24 and continued daily until PD 56. In adulthood (PD 70), animals were tested on measures of activity (figure-8 maze, open field test: OFT), anxiety (elevated-plus maze: EPM), and memory (novel object recognition: NOR). A subset of animals was sacrificed at PND 70, in the absence of behavioral testing, for tissue harvesting.AIE reduced activity (figure-8 maze, distance moved in EPM) in male but not female animals. The AIE-induced reduction in activity was prevented by choline supplementation only in the figure-8 maze. Additionally, in the OFT, males exposed to AIE spent less time in the center, suggesting elevated anxiety and/or reduced risk-taking, and this was prevented by choline supplementation. In females, we have previously found that AIE increased risk-taking behaviors (increased open arm time on the EPM), an effect that was both replicated in the present study and prevented by choline

supplementation. Finally, in both sexes, AIE significantly reduced the discrimination index in the NOR, indicating that AIE exposure impairs memory functioning. At sacrifice, dietary choline, AIE and their interaction were found to sex-dependently affect organ weight, fat content, and the liver enzyme alanine transferase. Investigations of cholinergic function in the medial prefrontal cortex, dorsal hippocampus and basal forebrain are ongoing. The prevention of AIE effects by choline supplementation is consistent with AIE-induced changes to the cholinergic system and suggests a potential agent to prevent AIE effects.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

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Program #/Poster #: PSTR296.06/RR18

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH P60 AA011605
NIH U24 AA020024

Title: Adolescent alcohol-induced changes in parvalbumin-expressing neurons and perineuronal nets in the anterior insula statistically mediate differences in behavioral flexibility in female and male rats

Authors: E. D. K. SULLIVAN[1], C. A. DANNENHOFFER[2], E. VIDRASCU[3], G. A. GOMEZ ACOSTA[4], B. SUTHERLAND[5], V. A. MACHT[4], F. T. CREWS[2], C. A. BOETTIGER[5], ***D. L. ROBINSON**[1];
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Abstract: When adolescents drink alcohol, they often binge drink, which can lead to long-lasting changes in brain and behavior. One consequence of adolescent binge alcohol in humans and rodents is reduced cognitive flexibility, or the ability to adapt one's strategy in response to changing circumstances. Using a rat model, we found that adolescent intermittent ethanol (AIE) exposure impaired reversal learning in an attentional set shift task and reduced functional connectivity among cortico-striatal-thalamic circuits measure by resting-state fMRI. Parvalbumin-expressing (PV+) GABAergic interneurons are critical for cortical excitatory-inhibitory balance and gamma oscillations that are thought to contribute to neural coupling between brain regions, with the anterior insula as one such region that acts as a hub switch among functional connectivity networks. Thus, we used immunohistochemistry to evaluate PV+ neurons in the anterior insula in rats that underwent reversal learning. We also evaluated

perineuronal nets (PNNs), which surround PV+ and other neurons and are dynamic extracellular structures that help maintain synapses and regulate extracellular ion concentrations. Based on ours and others' previous studies, we predicted that AIE exposure would promote increases in size and/or counts of PV+ neurons and PNNs, and this neurochemical change would be associated with behavioral deficits in reversal learning. To test this, male and female Sprague Dawley rats underwent AIE (5 g/kg via gavage) or volume-matched water control (CON) from postnatal day 25-54 on a 2-day-ON/2-day-OFF regimen (n = 8-10 per group). Rats underwent behavioral training in adulthood, including reversal learning on an attentional set shift task. Immunofluorescence (IF) was performed in the aIC to visualize PV+ interneurons and binding of WFA, a marker of PNNs. We found that AIE significantly increased the number of PV cells in the aIC of female and male rats. Additionally, PNN numbers were significantly increased in the AIE groups, as well as the proportion of PV cells surrounded by PNNs. Finally, we ran a principle component (PC) analysis on the IF parameters to reduce the dimensionality of the data into three PCs. The third PC accounted for 14% of the variance in IF parameters and was heavily weighted by the number of PNNs (0.856) and the proportion of PV+ neurons surrounded by PNNs (0.864), and this PC significantly mediated the effect of AIE exposure on behavioral flexibility measurements, specifically reversal 2 total trials. These results suggest that AIE may alter excitatory/inhibitory balance in the aIC via changes in PV interneuron number and their regulation by PNNs.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.07/RR19

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant P60 AA011605
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Title: Investigating differences in reversal learning and set shifting in adolescent intermittent ethanol-exposed and control-exposed Parvalbumin-Cre rats

Authors: *S. GARRISON[1,2], E. D. SULLIVAN[2], A. S. KUMAR[2], S. GIANG[2], C. A. BOETTIGER[2], D. L. ROBINSON[2];
[1]Pharmacol., Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [2]Bowles Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Adolescent binge alcohol consumption is a widespread issue with 8.3% of youth between the ages of 12 to 20 reporting at least one binge (defined as 4 drinks for girls and 5 drinks for boys) over the past month in 2021. Of these youth, 19% reported heavy alcohol use, meaning five or more binge incidences in the last month. Binge drinking in adolescence is a major concern due to the vulnerability of the brain during development, subsequent long-term cognitive effects that can emerge in adulthood, and an increased chance of developing dependence or addiction. These deficits can lead to various negative consequences in adulthood, including an increase in risk-taking behaviors, impaired judgment, and cognitive impairments. Cognitive flexibility, or the ability to adapt to change and switch from one task to another, is one aspect impacted by adolescent alcohol use. Using an animal model, we investigated adolescent intermittent ethanol (AIE) impact on cognitive flexibility measured via an attentional set-shifting task (ASST), a behavioral assay used to assess behavioral flexibility. Rats underwent a nine-day experimental protocol where they were trained to learn a set of rules applied to cues. Rats needed to differentiate between relevant cues (odors) and irrelevant cues (digging media) with a number of intra-dimensional and extra-dimensional set shifts where the rules were changed. In this study, we used PV-Cre rats to explore how AIE exposure across adolescence (P25-54) can lead to deficits in adulthood (P81-P114). Additionally, we compared results to those from previous Robinson lab ASST experiments to see if increasing the criterion of correct trials from 6 to 8 would reveal more robust differences between AIE and control subjects. Our preliminary data show untreated rats can learn the task despite the more challenging criterion, and the initial reversal of the ASST led to more errors (7±2) than a second reversal (4±1) or an extradimensional set shift (2±1). Ongoing studies are adding data from AIE-exposed male and female rats, where we expect AIE rats to learn rule associations like controls but have deficits in reversal learning. Future directions include the manipulation of parvalbumin-expressing (PV+) interneurons using Cre-dependent excitatory and inhibitory DREADDs to interrogate the role of prefrontal PV+ interneurons in behavioral flexibility as these neurons regulate synaptic plasticity and neural synchrony.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant P20GM103430

Title: Investigating the Role of Drosophila Dorsal Paired Medial (DPM) Neurons in Alcohol-Associated Memories

Authors: *E. CORTEZ[1], K. M. SCAPLEN[1,2];
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Abstract: Alcohol use disorder (AUD) is a chronic relapsing disorder that manifests as problematic patterns of alcohol use. At the core of AUD's behavioral manifestations is alcohol's profound effect on the brain. Alcohol engages and ultimately subordinates memory circuits resulting in enduring preferences, habitual behaviors, and persistent cravings. Insight to the circuit mechanisms that underlie how alcohol-associated memories are encoded, maintained, and expressed is critical to understanding why these memories are remarkably resistant to change. However, understanding the circuit basis of reward-related learning and addiction has been challenging. Efforts are often hindered by the neuronal heterogeneity that exists within dopamine (DA) sub-regions, as well as the lack of spatial and temporal resolution to distinguish neuronal subpopulations or isolate individual neurons. Drosophila melanogaster is a powerful model organism to address these challenges because they offer a rich genetic toolkit that permits dissection of heterogenous circuits with precise temporal and spatial resolution. Importantly, Drosophila form persistent alcohol reward memories, which impel them to overcome aversive stimuli in pursuit of alcohol-associated cues. Previous work identified discrete circuits that underlie alcohol reward memories and their temporal requirements. In Drosophila alcohol reward memory requires the mushroom body (MB), a region essential for learning and memory as well DA modulation of the MB which shifts from an entire population during acquisition to two discrete DA subsets known to process memories with opposing valences. However, it remains unclear the mechanisms by which these memories are consolidated. The Dorsal Paired Medial neurons (DPM), which innervate the MB have an established role in sleep regulation and memory consolidation. Using neurogenetic tools available in Drosophila we investigated the role of DPM neurons in alcohol reward memories and other alcohol associated behaviors. We utilized a transcriptional reporter of intracellular calcium (TRIC) to measure DPM neuronal activity and report postsynaptic targets using trans-Tango. Preliminary data suggest that DPM is required for the consolidation of alcohol reward memories, but not acquisition or retrieval. These findings provide insight to the circuit mechanisms underlying alcohol associated memories and why they are so resistant to change.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant P20GM103430
Rhode Island Foundation Medical Research Fund 20210957

Title: Mapping dopaminergic neural substrates of alcohol-associated behaviors in drosophila

Authors: *K. D. CALDARONE[1,2], S. L. SONG[3], N. T. SAVORY[3], E. CORTEZ[1,2], K. R. KAUN[3], K. M. SCAPLEN[1,2,3];
[1]Dept. of Psychology, [2]Ctr. for Hlth. and Behavioral Sci., Bryant Univ., Smithfield, RI; [3]Dept. of Neurosci., Brown Univ., Providence, RI

Abstract: Dopamine has an established role in a variety of processes including motivation, reward, and regulation of goal-directed and motor-related behavior across species. Furthermore, dysregulation of dopamine is thought to underlie the effect of alcohol and other drugs of abuse resulting in modified reward circuits. Given the heterogeneous role of dopamine, it is essential to gain a better mechanistic understanding of dopamine regulation and how its regulation is disrupted in maladaptive states, like those associated with alcohol. *Drosophila melanogaster* is a powerful model organism to investigate the neural dynamic changes that create persistent drug-related memories for alcohol intoxication and underlie alcohol-associated behaviors because of the excellent genetic tools that provide unprecedented spatial and temporal resolution. Previous work in *Drosophila* identified distinct dopamine circuits that underlie alcohol-associated memories and defined their temporal requirements (Scaplen et al., 2020). More recent evidence suggests that subsets of dopamine neurons (DANs) also mediate alcohol-induced locomotor activity. Here we use a multipronged approach that combines behavior, thermogenetic, and high-content behavioral analysis and take advantage of the precise circuitry of the mushroom body to investigate whether distinct DANs implicated for alcohol reward are also important for modulating locomotor responsiveness to alcohol. Preliminary data demonstrated that different subsets of DANs innervating the Mushroom Body play dynamic roles in modulating alcohol induced locomotor activity. Inactivation of DANs has the most substantial effects in late stages of alcohol exposure at high doses. We hypothesize more DANs are recruited during later stages of alcohol intoxication to counteract the sedating effects of alcohol. High-content behavioral analysis using Flytracker and Ctrax, post-processing computer vision software, suggests that distinct subsets of DANs modulate alcohol associated behavioral features characterized by fly activity, coordination, interaction, and social clustering. Interestingly, DAN subsets that are required for retrieval of alcohol reward memories do not appear to be required for alcohol-induced locomotor activity. We also describe the influence of DANs on locomotor activity in the absence of alcohol. Overall, this study clarifies the dose-dependent manner DANs mediate locomotor activity in *Drosophila* and is a starting point for further investigation of the mechanism in which drugs of abuse coops natural reward pathways and contribute to addiction.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant RO1AA028070
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Title: Nucleus accumbens BDNF-TrkB mediated encoding of ethanol reward

Authors: *A. N. SICLAIR[1], P. N. MCKEON[2], M. H. PATTON[2], E. B. ABEL[2], E. A. DOUGLASS[2], S. H. SHEATS[2], B. N. MATHUR[2];
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[2]Pharmacol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The nucleus accumbens (NAc) integrates many inputs to enable cue-reward associations. Our lab previously identified a form of inhibitory long-term depression in the NAc (NAc-iLTD) that requires brain derived neurotrophic factor (BDNF) signaling via the tyrosine kinase B (TrkB) receptor. This form of plasticity is enhanced by ethanol in a TrkB-dependent manner. This positions ethanol to disinhibit the NAc and, thereby, enhance reward encoding. Testing this idea, we found that dopaminergic terminals in the NAc serve as a sufficient and necessary source of BDNF to drive NAc-iLTD. In vivo, we show that light activation of the dopaminergic terminals in the NAc - in a manner that induces NAc-iLTD ex vivo - drives a conditioned place preference in a TrkB receptor-dependent manner. Coupling a subthreshold light activation of dopaminergic terminals and a subthreshold rewarding dose of ethanol also elicits a TrkB receptor-dependent conditioned place preference. These data suggest that ethanol interacts with BDNF-TrkB signaling in the NAc to mediate ethanol reward.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant AA028070
NIH Grant AA024845

Title: Chronic Intermittent Ethanol disturbs claustrum neuronal activity

Authors: *A. B. WULFF[1], S. H. SHEATS[1], E. A. DOUGLASS[2], B. N. MATHUR[1];
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Abstract: Alcohol Use Disorder (AUD) is a prevalent disorder affecting more than 10% of adults in America and comprising more than 5% of the global burden of disease and injury. Prior

research strongly points to a bidirectional relationship between impaired cognitive control and heavy alcohol use, suggesting a mechanism for the development and exacerbation of AUD. While recent studies point to the claustrum as a locus for orchestrating synchronized cortical activity required in cognitive control, it is yet unknown how claustrum activity is affected by alcohol exposure.To determine whether claustrum neuronal activity is affected by chronic alcohol exposure we performed whole-cell patch clamp recordings in claustrum-containing brain slices from mice subjected to either chronic intermittent vaporized ethanol or chronic intermittent air (water vapor). We found that claustrum neurons from ethanol-exposed mice exhibited perturbed intrinsic excitability and action potential properties that may lead to over-excitable claustrum neurons. We further found subtle changes in passive membrane properties suggestive of dendritic reorganization.
These findings suggest that chronic ethanol exposure may lead to profound and widespread changes in claustrum neuronal activity that may mediate alcohol-induced impairments to cognitive control.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

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Program #/Poster #: PSTR296.12/SS4

Topic: G.09. Drugs of Abuse and Addiction

Support: NIAAA R01 AA019454-12
NIAAA K99 AA030628-02

Title: The Bed Nucleus of the Stria Terminalis 5HT2c receptor system sex-dependently suppresses compulsive alcohol seeking

Authors: *M. FLANIGAN[1], M. CASTLE[2], C. A. GIANESSI[1], W. DORLEAN[2], V. SIDES[1], T. KASH[3];
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Abstract: The serotonin $5HT_{2c}$ receptor has been widely implicated in the pathophysiology of Alcohol Use Disorder (AUD), particularly alcohol seeking and the affective consequences of chronic alcohol consumption. However, very little is known about the specific brain sites in which $5HT_{2c}$ exerts its effects on specific alcohol-related behaviors, especially in female subjects. Here, we investigated the effects of site-specific knockdown of the $5HT_{2c}$ receptor in the BNST on operant alcohol self-administration behaviors in adult mice of both sexes, including alcohol seeking (fixed-ratio responding), motivation for alcohol (progressive ratio), and quinine-adulterated alcohol seeking (compulsive alcohol seeking). To dissociate the effects of $5HT_{2c}$

knockdown from the effects of reducing the activity of $5HT_{2c}$-containing neurons, we carried out the same operant alcohol self-administration behavioral sequence while performing chemogenetic inhibition of BNST $5HT_{2c}$-containing neurons. We report that BNST knockdown of $5HT_{2c}$ did not affect alcohol seeking or progressive ratio responding for alcohol in either sex. While BNST $5HT_{2c}$ knockdown drove perseverant operant responding for 1000 μM quinine alcohol selectively in females, this manipulation did not promote increased consumption of quinine alcohol. Chemogenetic inhibition of BNST $5HT_{2c}$-containing neurons ($BNST^{5HT2c}$) increased fixed-ratio responding for alcohol and alcohol consumption in early self-administration sessions, particularly in males. It also increased operant responding for 1000 μM quinine alcohol in males. However, similar to results of $5HT_{2c}$ deletion in females, chemogenetic inhibition of $BNST^{5HT2c}$ did not alter the actual amount of quinine alcohol consumed in males. Importantly, chemogenetic inhibition of $BNST^{5HT2c}$ did not alter sucrose seeking, motivation for sucrose, or compulsive sucrose seeking in either sex. Immunohistochemistry combined with chemogenetics revealed that $BNST^{5HT2c}$ project to similar regions in males and females, but that inhibition of $BNST^{5HT2c}$ reduces vlPAG activity selectively in males. Given the role of the vlPAG in generating aversive behavioral responses, we therefore describe a potential new role for $BNST^{5HT2c}$ in generating increased aversion to alcohol-related stimuli via activation of the vlPAG in males. Together, these results demonstrate that the BNST $5HT_{2c}$ receptor system is engaged in sex-specific ways to selectively modulate compulsive alcohol seeking and vlPAG activity while only weakly influencing alcohol consumption itself.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.13/SS5

Topic: G.09. Drugs of Abuse and Addiction

Support: F32 AA030494
T32 AA007573
U24 AA025475

Title: Septohypothalamic nociceptin/orphanin-fq receptors modulate binge-like alcohol consumption.

Authors: *H. HAUN[1], L. YAN[1], R. HERNANDEZ[2], T. L. KASH[3];
[1]Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [2]Morgan Community Col., Fort Morgan, CO; [3]Bowles Ctr. for Alcohol Studies, UNC-Chapel Hill, Chapel Hill, NC

Abstract: Excessive alcohol consumption is a hallmark of Alcohol Use Disorder (AUD) and presents as a major public health concern. To curb excessive drinking behavior, antagonists

targeting the opioid-like nociceptin receptor (NOP) have shown promise in reducing heaving drinking in patients with an AUD, and reduce alcohol intake in preclinical models. We have previously identified the lateral septum (LS) to be enriched in neurons expressing the endogenous ligand to NOP, nociceptin/orphanin-fq (N/OFQ), and found that these neurons ($LS^{N/OFQ}$) bidirectionally regulate alcohol consumption in male and female mice. The present studies were designed to functionally map $LS^{N/OFQ}$ projections, and determine the contribution of NOP therein to excessive alcohol consumption. Pnoc-cre mice were used to direct expression of AAV8-DIO-Synaptophysin-mCherry to $LS^{N/OFQ}$, and terminal fields were observed locally within the LS, and downstream in the lateral hypothalamus (LH) and supramammillary nucleus of the hypothalamus (SuM). Channelrhodopsin-assisted circuit mapping was then conducted to determine functional connectivity of $LS^{N/OFQ}$ in these projection fields. Briefly, slices containing the LS, LH, or SuM were collected and incubated in aCSF and inhibitory post synaptic currents (IPSCs) were isolated, given that $LS^{N/OFQ}$ is a GABAergic population. Recordings were collected from each structure during blue light stimulation and picrotoxin-sensitive optically evoked IPSCs were observed from synaptic targets of $LS^{N/OFQ}$ in the LS, LH, and SuM, indicating functional GABAergic synapses. We then used the Drinking-in-the-Dark (DID) paradigm to model binge-like alcohol consumption, and used a genetic deletion strategy to determine a functional role for NOP in the LS, LH, and SuM in binge drinking. Male and female NOP*fl/fl* mice received bilateral infusion of AAV8-hSyn-cre (or GFP) into the LS, LH or SuM, and mice were given access to alcohol (20%; v/v, 2hr) for 3 weeks. Male mice lacking the NOP receptor in the LS displayed decreased binge-like alcohol intake compared to controls (-23%; P=0.016), while drinking in females remained unaffected. Genetic deletion of NOP from the LH reduced alcohol intake in females (-19%; P=0.011), without affecting drinking in males. Preliminary findings (N=3-5/sex/AAV) indicated that NOP deletion from the SuM reduced alcohol intake in female mice (-16%; P=0.03), with no effect in males. In summary, these findings demonstrate novel functional $LS^{N/OFQ}$ projections to the LS, LH, and SuM, and highlight important sex differences in the ability of NOP to regulate binge drinking behavior.

Disclosures: **H. Haun:** None. **L. Yan:** None. **R. Hernandez:** None. **T.L. Kash:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.14/SS6

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant 2T32AA007573-26
NIH Grant 5U01AA020911-12

Title: Effects of acute and chronic alcohol consumption on extended amygdalar calcium dynamics

Authors: *A. ROLAND[1], T. KASH[2];
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Abstract: The central amygdala (CeA) and bed nucleus of the stria terminalis (BNST) are reciprocally connected nodes of the extended amygdala that are differentially engaged during initial alcohol consumption and following withdrawal from chronic drinking. Studies of immediate-early genes indicate that BNST and CeA are acutely activated following alcohol drinking and may promote alcohol reward in nondependent drinkers, while increased stress signaling in the extended amygdala following chronic alcohol exposure promotes relapse drinking via negative reinforcement. However, the dynamics of neural activation in BNST and CeA during drinking behavior are unknown. In this study, we used fiber photometry and the genetically encoded calcium sensor GCaMP to assess acute changes in neural activity during alcohol consumption in BNST and CeA before and after a chronic drinking paradigm. Activity was examined in the pan-neuronal population and separately in genetically defined dynorphinergic neurons. BNST and CeA showed strongly synchronized pan-neuronal activity and coordinated increases in activity during acute consumption of alcohol as well as other fluid tastants of both positive and negative valence, as well as highly palatable chow. Calcium increases were greatest during the initial consummatory bout and decreased in amplitude with repeated consumption of the same tastant, indicating modulation of the response by the novelty of the stimulus. Dynorphin neurons showed similar consumption-associated calcium increases in both brain regions. Following a three-week continuous access (CA) alcohol drinking paradigm, both pan-neuronal and dynorphinergic calcium increases during drinking were maintained, but the initial response to alcohol in the CeA was reduced compared to the pre-CA baseline. These results indicate that the extended amygdala, and dynorphin neurons specifically, are engaged during consummatory behavior and suggest that stimulus novelty may influence the activity of these regions.

Disclosures: **A. Roland:** None. **T. Kash:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.15/SS7

Topic: G.09. Drugs of Abuse and Addiction

Support: T32AA007573
P60011605

Title: A role for the retrosplenial cortex in heightened adult fear expression following binge-like alcohol exposure during adolescence

Authors: L. TAXIER[1], L. COLEMAN[2], ***T. KASH**[3];
[1]Univ. of North Carolina-Chapel Hill, Chapel Hill, NC; [2]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]UNC- Chapel Hill, Chapel Hill, NC

Abstract: Adolescent binge drinking increases risk for developing an Alcohol Use Disorder (AUD) and other comorbid conditions in adulthood, including anxiety and post-traumatic stress disorders (PTSD). Yet, how adolescent binge drinking engenders such negative health outcomes remains largely unknown. Here, we tested the hypothesis that binge-like alcohol exposure during adolescence (AIE) promotes aberrant fear expression in adulthood, and that AIE-heightened fear is linked to altered function of the retrosplenial cortex (RSC), a region critical for retrieval of episodic-like fear memory. Male and female C57Bl/6 mice underwent a regimen of water or AIE via gavage during adolescence (P25-P55), followed by trace fear conditioning in adulthood (P90). All mice acquired fear to a similar extent, suggesting that AIE did not alter fear acquisition. However, during fear retrieval, AIE-exposed mice of both sexes froze more than water controls, suggesting that AIE promotes heightened retrieval of a trace fear memory. In a separate cohort of male C57Bl/6 mice that underwent water or AIE, slices containing the RSC were prepared to assess intrinsic excitability using whole-cell patch clamp electrophysiology. AIE-treated males exhibited a higher rheobase, or minimum current required for an action potential to fire, relative to water controls. Combined, these data suggest the possibility that reduced intrinsic excitability in the RSC may be a contributing mechanism to altered fear expression following AIE.

Disclosures: L. Taxier: None. **L. Coleman:** None. **T. Kash:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.16/SS8

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R37AA019455
NIH Grant DK106476

Title: Adolescent-onset voluntary ethanol consumption and subsequent negative affective behavior and whole brain cFos expression during forced abstinence in mice

Authors: *C. M. EDWARDS[1,2], R. B. SIMERLY[1,2], D. G. WINDER[1,2];
[1]Mol. Physiol. & Biophysics, [2]Vanderbilt Ctr. for Addiction Res., Vanderbilt Univ., Nashville, TN

Abstract: Negative affect experienced during abstinence from alcohol can significantly contribute to relapse and the development of alcohol dependence. In particular, chronic alcohol use during adolescence poses a substantial risk for the later development of alcohol use disorder. This study aimed to investigate the voluntary consumption of ethanol and its impact on negative

affective behavior, as well as associated neural changes, in mice that initiated ethanol consumption during early adolescence (~PND30). Male and female adolescent C57BL/6 mice went through the Chronic Drinking Forced Abstinence (CDFA) paradigm in which half of the mice ("Ethanol" group) were given two-bottle choice between ethanol and water whereas the control mice ("Water" group) were given two bottles containing water. In Experiment 1, ethanol bottle weights were manually recorded to measure ethanol intake (g/kg/day) and ethanol preference over a six-week period. Subsequently, the bottles were removed, and two weeks later, the animals underwent several behavioral tests to evaluate negative affect, including the light/dark box, elevated plus maze, forced swim test, and novelty suppressed feeding test. While female C57BL/6 mice prefer and consume more ethanol than males as adults, we found that male and female mice that began drinking during early adolescence consume similar levels of ethanol and display similar preference for ethanol over water. We also observe negative affective behaviors in mice during forced abstinence. In Experiment 2, ethanol intake was assessed using the Lick Instance Quantifier (LIQ) system, enabling a more precise measurement of ethanol consumption behavior, including lick number and lick duration. Additionally, brains were collected at 24 hours and 2 weeks into forced abstinence and analyzed for regionally specific changes in whole brain cFos expression. Adolescent onset of CDFA provides a translationally relevant model of negative affect following chronic alcohol consumption and could provide interesting insight into neural circuitry underlying the development of alcohol use disorder.

Disclosures: C.M. Edwards: None. **R.B. Simerly:** None. **D.G. Winder:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.17/SS9

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R37AA019455

Title: Neural adaptations in the insular cortex following abstinence from chronic ethanol exposure

Authors: P. YOUNG[1], A. TAYLOR[2,1], D. ADANK[2,1], ***D. WINDER**[2,1];
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Abstract: The insular cortex (IC) is a brain region that integrates sensory and interoceptive cues to inform downstream circuitry executing adaptive behavioral responses. The IC communicates with areas involved canonically in stress and motivation, and lesion analyses heavily implicate the region in addiction. Studies from a number of groups implicate the IC in alcohol use disorder (AUD), particularly during periods of withdrawal and forced abstinence. Using a mouse model of AUD known as chronic drinking forced abstinence (CDFA), we examined molecular changes

in the IC following acute and protracted abstinence from chronic alcohol exposure. Following a 6-week voluntary drinking period, we collected tissue containing the IC and performed *in situ* hybridization analyses to test the hypothesis that potassium channels previously demonstrated as ethanol sensitive were altered in their expression. We assessed potassium channel mRNA expression 24 hours and 2 weeks into forced abstinence. Informed by previously collected data indicating changes in neuronal excitability at these timepoints, we looked at three potassium channels in this region: BK, SK, and A-Type channels. After determining that BK mRNA was the most abundant in the IC, we assessed whether its expression changed following CDFA. Analysis revealed significant differences in BK mRNA expression during acute abstinence compared to control and protracted abstinence. Additionally, we identified the cell types in the IC that exhibit the highest enrichment of BK by quantifying BK mRNA expression colocalized with mRNA expression of vGlut1, somatostatin, and parvalbumin. We counted significantly fewer BK puncta in all cell types in the 24hrs FA group. Using whole cell patch clamp electrophysiology and BK channel pharmacology in control mice, we found that the antagonist paxilline mimicked elevated firing patterns in seen in the IC of 24hrs FA subjects. These results may inform identification of new therapeutic targets as well as potential timing for recovery treatments.

Disclosures: **P. Young:** None. **A. Taylor:** None. **D. Adank:** None. **D. Winder:** None.

Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.18/SS10

Topic: G.09. Drugs of Abuse and Addiction

Support: AA029592
NS007491
MH065215
AA019455

Title: Aversion resistant ethanol intake and seeking: A step towards understanding vulnerable subpopulations in Alcohol Use Disorder using a C57BL/6J mouse model

Authors: *M. DOYLE, A. S. PARK, M. E. ALTEMUS, M. E. TROUTMAN, D. N. ADANK, L. LANTIER, C. A. SICILIANO, D. G. WINDER;
Vanderbilt Univ., Nashville, TN

Abstract: In the Alcohol Use Disorder (AUD) treatment seeking population, periods of abstinence define a highly vulnerable portion of the AUD cycle, as during this time individuals report heightened craving and experience increased negative affect. Given the heterogeneity of alcohol use and behaviors observed in the clinical population, animal models highlighting individual differences may provide novel insight to the development of targeted therapeutic

interventions. Here, we used an operant conditioning task known as Structured Tracking of Alcohol Reinforcement (STAR) to assess changes in ethanol intake and aversion resistance following a forced abstinence period. Male and female C57BL/6J mice were trained to self-administer a 20% ethanol solution via a retractable sipper. Following a training period, mice self-administered ethanol in daily 1-hour sessions for 14 days before starting a forced abstinence period (28 days). Mice then underwent the STAR procedure. Here, mice were returned to ethanol self-administration for 3 days before increasing concentrations of quinine (0.25, 0.5, 0.75, and 1.0 mM) were added to the ethanol to assess aversion-resistant (compulsive) intake behaviors. Under this assay, mice reliably segregate into high, low, or compulsive drinking phenotypes. Critically, our data suggest that compulsive drinkers may represent a particularly vulnerable subpopulation, exhibiting greater ethanol seeking in protracted abstinence compared to high and low drinking mice. Additionally, we found that females largely grouped into high drinkers while males primarily categorized as compulsive drinkers, revealing an intriguing sex difference in compulsive ethanol intake. Because the bed nucleus of the stria terminalis (BNST) is known to undergo plastic changes during forced abstinence following ethanol exposure, we next used in vivo fiber photometry to record BNST GCaMP transients as a method of assessing changes in BNST activity across operant sessions. Preliminary data suggest increased BNST activity across all STAR drinking phenotypes during the initial ethanol intake sessions; however, only compulsive drinking mice showed persistent BNST activation during ethanol seeking, highlighting an intriguing maladaptive involvement of the BNST in this vulnerable phenotype. These recordings may yield insights into sex differences in BNST adaptations, and future directions seek to identify BNST specialized neuronal subtype(s) that drives these effects.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.19/SS11

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R37AA019455
NIH Grant F31AA030901

Title: Motor cortex control of the insular cortex as a target for exercise-alcohol interactions

Authors: *D. N. ADANK[1,2], A. TAYLOR[1,2], N. PETERSEN[1,2], Y. QUAN[2], J. R. LUCHSINGER[1,2], D. G. WINDER[1,2];
[1]Mol. Physiol. and Biophysics, [2]Vanderbilt Ctr. for Addiction Res., Vanderbilt Univ., Nashville, TN

Abstract: Alcohol use disorder (AUD) is a chronic relapsing condition often driven by negative affective states. We and others have demonstrated in mice that voluntary wheel running can ameliorate negative affective states during alcohol abstinence. The insular cortex (IC) has emerged as an essential driver of negative affect through interconnections with the bed nucleus of the stria terminalis (BNST). We have previously shown the IC as a critical player in negative affective behaviors that arise during alcohol-forced abstinence and in active coping bouts during restraint stress in mice. Intriguingly, we found that IC activity decreases during voluntary wheel running in mice. Our previous mapping studies established somatomotor cortical areas as major afferents to IC neurons that project to the BNST. Active coping events during stress are associated with the activation of insular projection neurons. These bouts were also associated with transient reductions in extracellular GABA levels. IC GABA is a regulator of chronic stress adaptation, suggesting the possibility that somatomotor afferents impinge on interneuron populations in IC. We utilized anterograde and retrograde tracing approaches to test the hypothesis that primary motor cortex (MOp) afferents also innervate interneuron populations in the IC. Our convergent data suggest that MOp projections synapse onto GABAergic somatostatin (SST) cells in the IC. We then used channelrhodopsin-assisted mapping to demonstrate functional excitatory transmission between MOp-IC^{SST}. While acute ethanol does not greatly influence the basal excitability of IC^{SST} cells, it reduces excitatory transmission from MOp afferents onto these cells. These findings suggest the MOp-IC^{SST} as a novel circuit to explore in exercise modulation of alcohol-related behaviors.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.20/SS12

Topic: A.09. Adolescent Development

Title: Exposure to Chronic Intermittent Ethanol Vapor in Adolescence Differentially Affects Consummatory and Appetitive Behavior in Response to a Non-Drug Reward in Adulthood

Authors: *C. MAJORS, C. M. MARKS, D. C. PATEL, P. I. INSCORE, G. A. DEEHAN, Jr.; East Tennessee State Univ., Johnson City, TN

Abstract: Alcohol-use disorders affect 15 million people nationwide, 4% of which are adolescents (12-17). Clinical data indicate that adolescents who binge drink greatly increase their likelihood of developing an alcohol-use disorder later in life. Moreover, research indicates that binge-drinking during adolescence produces long-lasting alterations in brain circuitry that underlie the processing of rewarding stimuli. The current study sought to determine the effect of adolescent exposure to chronic intermittent ethanol (CIE) on the consumption of, and motivation to obtain, sucrose solution in adulthood. Alcohol naïve, male Wistar rats arrived at the laboratory

on post-natal day (PND) 25 and were randomly divided into two exposure groups (CIE and Air). Animals were provided 3 days to allow for acclimation to the animal colony, prior to the start or experimental procedure (PND 28). The CIE procedure involves inducing alcohol dependence by placing rats, in their home cage, into an alcohol vapor chamber for 14 consecutive days, with each exposure day consisting of 12 hrs of exposure in the chambers (8 am to 8 pm) and 12 hrs out of the chambers. The control rats (Air) are treated the same as CIE rats but without exposure to ethanol vapors. Following the CIE paradigm, all rats remained in their home-cage until adulthood (>PND 70) at which time they started operant training/testing in standard operant chambers equipped with two sipper tubes connected via tubing to liquid delivery solenoids. When the response requirement (# of licks) was met, animals received a delivery of 0.1 ml of 5% sucrose solution. All animals were instrumented to the operant procedure on a fixed-ratio (FR) 2 schedule which increased to an FR4 then FR8. Finally, all rats underwent a progressive ratio test in which response requirement increased exponentially for each liquid delivery. On lower schedules (FR2 and FR4) animals did not exhibit a significant difference in licks or reinforcers earned. However, for higher schedules (FR8 and PR) animals in the Air group exhibited a significantly higher level of behavior (licks) and received a significantly greater number of reinforcers than the CIE group. Overall, the data suggest that exposure to CIE, which approximates binge-like EtOH intake and dependence, differentially affects consummatory and appetitive behavior in response to a non-drug reward in adulthood.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.21/Web Only

Topic: F.03. Stress and the Brain

Support: Fundación Florencio Fiorini
UBACYT 20020190100222BA

Title: Effects of ethanol consumption and noise exposure during adolescence on hippocampal-related behaviors

Authors: L. C. ARAUJO AÑON[1], G. CORSI[1], S. MARCOS[1], F. J. MICHALINA[1], G. E. BUJÁN[2], L. D'ALESSIO[3,2], L. R. GUELMAN[1,2], *S. J. MOLINA[4];
[1]Univ. de Buenos Aires. Consejo Nacional de Investigaciones Científicas y Técnicas. Ctr. de Estudios Farmacológicos y Botánicos (CEFyBO, UBA-CONICET)., Buenos Aires, Argentina; [2]Univ. de Buenos Aires. Facultad de Medicina. 1ª Cátedra de Farmacología, Buenos Aires, Argentina; [3]Univ. de Buenos Aires. Consejo Nacional de Investigaciones Científicas y Técnicas. Inst. de Biología Celular y Neurociencias (IBCN, UBA-CONICET)., Buenos Aires, Argentina;

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Abstract: Adolescents frequently consume alcoholic beverages in entertainment venues such as discos and bars, where they are often exposed to high levels of noise. Animal studies have demonstrated that both ethanol (EtOH) and noise can cause damage to the hippocampus (HC), a brain region associated with memory and anxiety-related behaviors. However, there is limited information regarding the effects of noise on female rats. Thus, the aim of this work was to examine the effects of EtOH and noise exposure on HC-related behaviors in adolescent female rats. Female Wistar rats (28-days-old) were subjected to a two-bottle choice intermittent EtOH intake paradigm for a duration of 4 weeks. Additionally, during the 6th and 9th drinking sessions, a subgroup of rats were exposed to noise (95-97 dB, 2h). Finally, Open Field, Elevated Plus Maze and Object Location tasks were performed. The results revealed that noise exposure alone led to an increase in anxiety-like behaviors, while EtOH intake alone or in combination with noise decreased head dipping (a risk assessment behavior). Moreover, both stimuli separately or together resulted in a decrease in exploratory behavior. However, no significant differences were observed in spatial and habituation memories. These findings suggest that both exposure to noise and EtOH during adolescence are capable of causing changes in HC-related behaviors of female rats. On the one hand, the fact that EtOH intake promotes lower exploration and risk assessment behaviors could be dangerous since it implies less caution and greater exposure to potential dangers. On the other hand, increased anxious behavior and decreased exploration of the environment, as observed in noise-exposed rats, could result maladaptive in different situations. Finally, the combination of both stimuli does not generate greater behavioral changes than those observed in rats that only consumed EtOH. These findings are clinically relevant since they reproduce part of the behavioral alterations in human adolescents, resulting in an appropriate animal model to investigate in the future the mechanisms involved in hippocampal alterations.

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Poster

PSTR296. Chronic Ethanol Behavioral Effects: Adolescent and Adult

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR296.22/SS13

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant UL1TR002489-044
NIH Grant GM083980

Title: Sex differences in anxiety-like behavior, adolescent intermittent ethanol-induced drinking, and c-Fos in limbic brain structures in male and female C57BL/6J mice

Authors: T. DEAN[1], J. DENNIS[1], I. C. THOMAS[2], J. A. BAKER[2], K. A. SIMONTON[2], A. KUMARI[1], M. J. SHOBANDE[3], C. E. EMEHEL[1], R. CANNADY[1], ***A. M. MALDONADO-DEVINCCI**[2];
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Abstract: Adolescence is a period associated with increased binge drinking and long-term changes in brain and behavioral outcomes. Adolescent males and females are also motivated to drink alcohol by different factors including stress and coping for females and sociability for males. Indeed, in recent years binge drinking rates in adolescent females have surpassed that of adolescent males. In this experiment, we tested baseline sex differences in anxiety-like behavior during early adolescence and later tested adolescent intermittent ethanol-induced changes in voluntary alcohol drinking and subsequent withdrawal-induced changes in c-Fos, a marker for neuronal activation. During early adolescence (postnatal day (PND) 24) we observed an increased anxiety-like phenotype in females compared to males. When mice were exposed to adolescent intermittent ethanol (AIE; PND 28-44) and tested for subsequent recurrent ethanol drinking, we found that males and females showed increased ethanol drinking after AIE (PND 45-49) and after re-exposure (PND 52-73). This pattern was sustained over repeated cycles of ethanol re-exposure in males and dissipated in females over time. Brains were collected and AIE withdrawal-induced changes in c-Fos were observed across different limbic structures. Together, these data indicate that adolescent ethanol exposure increased subsequent ethanol drinking and neuronal activation in limbic structures is altered during withdrawal from ethanol re-exposure. Future work will incorporate cell-type specific markers to determine which types of cells are implicated in these lasting sex-specific effects.

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Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.01/SS14

Topic: G.09. Drugs of Abuse and Addiction

Support: Supported by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) under Award Number R43DA053055
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Title: Effect of DPI-125 on opioid withdrawal behaviors in rats: a comparison study with methadone and buprenorphine

Authors: B. GAMALLO LANA[1], B. JULIAN[2], E. VERSI[2], ***A. C. MAR**[3];
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Abstract: Opioid withdrawal syndrome, which comprises symptoms such as increased pain sensitivity and sickness-like behavior, is a major impediment in the treatment of opioid use disorder. While medication for opioid use disorder (MOUD) can reduce opioid use, a major hurdle for patients is the experience of withdrawal when transitioning to stable MOUD dose regimens, reducing the desire to initiate treatment. Prior evidence suggests that DPI-125, a small molecule triple (mu, delta and kappa) opioid receptor agonist, has safety and efficacy advantages over currently available MOUD agents in terms of reduced respiratory depression (delta agonism) and reduced likability (kappa agonism). In this study we examine the timing and effectiveness of DPI-125 in reducing symptoms of opioid withdrawal relative to traditional MOUD ligands, methadone and buprenorphine. Induction of analgesia was used to establish a comparative dose-response and time course for each test agent. Twenty male Sprague Dawley rats (250-325g, Envigo) were tested on the tail flick analgesia meter (IITC) at -1, 30, 60, 120, 180 mins after subcutaneous injection with vehicle, DPI-125 (0.25, 0.5 or 1.0mg/kg), buprenorphine (0.05 mg/kg) or methadone (2.5 mg/kg). Results indicated a dose-dependent analgesic effect of DPI-125, where 0.5mg/kg DPI-125 shows a similar peak and time course of analgesia as 2.5mg/kg methadone. To assess the comparative effects of DPI-125 on withdrawal-like symptoms, 48 rats were implanted subcutaneously with 2 x 75mg morphine pellets to induce opioid dependence with pellets then removed 8 days later. Control animals were treated identically but implanted with vehicle pellets. Body weight and tail flick assessment 24 hours after pellet implantation confirmed the acute hyperphagic and hypoalgesia effects of morphine treatment. 48 hours following pellet removal, rats were subcutaneously injected according to treatment group (veh-veh, morph-veh, morph-DPI-125[0.25,0.5,1.0mg/kg], morph-bup[0.05mg/kg], morph-meth[2.5mg/kg]) and were video recorded in an observation cylinder for 3 hours. Somatic signs of withdrawal (SSW) were assessed by two, blinded independent observers across three 15-min time periods. Body key points were also labelled and machine learning algorithms used to detect behavioral differences between treatment groups. Both 0.25mg/kg and 0.5mg/kg DPI-125 reduced the global number of SSW relative to morph-veh treated rats with the magnitude and time course again indistinguishable from reductions observed with 2.5mg/kg methadone treatment. These data suggest that DPI-125 might be a potentially useful MOUD to help improve outcomes in opioid use disorder.

Disclosures: B. Gamallo Lana: None. **B. Julian:** A. Employment/Salary (full or part-time):; Dr. Julian is employed by DMK Pharmaceuticals. 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.; Study was supported by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) under Award Number R43DA053055. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Commercial funds from DMK were used to supplement the direct costs of this work. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Julian holds an equity position in DMK Pharmaceuticals, DMK Pharmaceuticals owns or controls patents and other intellectual property rights relating to DPI-125 and is currently advancing it as a treatment for opioid use disorder. **E. Versi:** A. Employment/Salary

(full or part-time):; Dr. Versi is the chief executive officer of DMK Pharmaceuticals, Dr. Versi is employed by DMK Pharmaceuticals. 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.; Study was supported by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) under Award Number R43DA053055. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Commercial funds from DMK were used to supplement the direct costs of this work. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Versi holds an equity position in DMK Pharmaceuticals, DMK Pharmaceuticals owns or controls patents and other intellectual property rights relating to DPI-125 and is currently advancing it as a treatment for opioid use disorder. **A.C. Mar:** 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.; Study was supported by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) under Award Number R43DA053055.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Commercial funds from DMK were used to supplement the direct costs of this work.

Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.02/SS15

Topic: G.09. Drugs of Abuse and Addiction

Support: WSU Chair Startup Funds

Title: Gabaergic mediation of abstinence induced anxiety following repeated binge pattern toluene exposure in a murine model

Authors: D. SVENSON[1], T. BENDER[2], S. POINTE[2], ***S. BOWEN**[2];
[1]Psychology, [2]Wayne State Univ., Detroit, MI

Abstract: Inhalant abuse continues to be a serious world-wide problem and can inflict numerous pathological and neurobehavioral outcomes. The aromatic hydrocarbon toluene is one of the most widely abused inhalants and its inhalation produces neurobehavioral effects similar to CNS depressants. Abuse of toluene has also been shown to cause serious withdrawal effects. Previous work from our lab has shown that toluene can induce anxiety-like effects after prolonged exposure to high concentrations. The present study aimed to further explore the involvement of GABA and the amygdala in mediating the anxiogenic effects of toluene-abstinence. Adolescent male and female Swiss-Webster mice (N = 96) were exposed to either air (0 ppm) or toluene (4000 ppm) for 30 min/2x daily for 4 days. Twenty-four hours following the final toluene

exposure, all mice received i.p. injections of either saline, muscimol (0.5 mg/kg), or bicuculline (1 mg/kg) followed by a sham air exposure and tested immediately for changes in locomotor activity (LMA), followed by testing on the elevated plus maze (EPM) and marble burying test (MBT). Subsequently, animals were euthanized for assessment of c-Fos within the amygdala. Results showed that the first toluene exposure significantly increased LMA, which significantly tapered over the next 3 days until reaching control levels, suggesting a tolerance effect. Toluene-abstinence increased closed-arm time on the EPM in male mice only. This effect was rescued by muscimol. No significant differences were observed in the MBT. Further analyses with immunofluorescence showed that toluene produced decreases in c-Fos expression within the BLA of air/saline mice (male only) and an increase within the CeA of toluene-abstinent/muscimol mice (male only). Results from this study show an underlying GABAergic mechanism mediating the anxiety-inducing effects of toluene-abstinence following repeated binge-pattern exposure. These findings may further inform clinical practice and suggest a useful therapeutic target (i.e., GABA) in treating withdrawal-induced anxiety following toluene abuse.

Disclosures: **D. Svenson:** None. **T. Bender:** None. **S. Pointe:** None. **S. Bowen:** None.

Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.03/SS16

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH-FDA Grant U54DA036151

Title: Reinforcing and hedonic effects of the e-cigarette solvents propylene glycol and vegetable glycerin in male rats

Authors: *T. NELSON, N. A. ADDY, D. BAGDAS;
Yale Univ., New Haven, CT

Abstract: Propylene Glycol (PG) and Vegetable Glycerin (VG) are common solvents used as vehicles in e-cigarettes. PG and VG are also used as humectants, which are substances used to keep things moist, in combustible cigarettes and smokeless tobacco products such as oral nicotine pouches. Although tobacco product characteristics can affect nicotine use behaviors, the addictive potential of PG and VG are unknown. Therefore, we evaluated the potential reinforcing and orosensory properties of PG/VG in operant behavior and oral sensory paradigms. Male Sprague Dawley rats and PG/VG at 50/50 ratio were used throughout the study. Rats were exposed to PG/VG vapor in a combined passive and self-administration procedure in an e-cigarette vapor delivery system. During the passive administration phase, rats received a 3-second vapor puff every 8 minutes for a total of 15 vapes in one session. This phase continued for 5 days. Then, rats were allowed to self-administer PG/VG vapor (3-second puff with a 30-second timeout period) 1 hour daily. Rats completed 6 days of fixed ratio (FR)1, 5 days of FR3,

and 7 days of FR5 schedule, respectively. The vapor paired nose poke was identified as active response. Next, we used the intraoral self-administration paradigm in intraoral catheter-implanted rats. The rats were placed into the chambers where the PG/VG or water was connected to their intraoral catheters and the active lever press was connected to the test solution for a 1-hour session daily. Rats completed 5 days of FR1, 3 days of FR2, 7 days of FR5, and 1 day of progressive ratio schedule. Lastly, we investigated hedonic and aversive orosensory properties of PG/VG in the taste reactivity test. The animals received 20 random 4-s infusions of the PG/VG via their intraoral catheters over a 45-minute session. The face reactions of rats were recorded, and the videos were analyzed for their hedonic and aversive responses to the PG/VG and water control. Rats discriminated vapor/oral solution-paired active and non-paired inactive nose holes/levers. The active nose pokes were significantly higher than inactive nose pokes during vapor self-administration. Rats also showed significantly higher active lever presses compared to inactive lever presses and water control in the intraoral self-administration. Rats also had significantly higher hedonic taste responses to PG/VG compared to water control. Additionally, there were no differences in aversive taste responses between PG/VG and water. In summary, PG/VG has reinforcing potential, possibly due to its hedonic properties. Our future studies will clarify PG/VG's reinforcing potential in female rats and its effects on nicotine use behaviors.

Disclosures: T. Nelson: None. **N.A. Addy:** None. **D. Bagdas:** None.

Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.04/SS17

Topic: G.09. Drugs of Abuse and Addiction

Support: RSCA Grant
SARC Grant

Title: Examining the consequences of adolescent benzodiazepine exposure

Authors: *D. PAPASERGIA[1], S. BATES[2];
[2]Psychology, [1]CSU Chico, Chico, CA

Abstract: *Background:* Benzodiazepines are commonly used to treat anxiety disorders. However, in the past decade the intentional abuse and misuse of benzodiazepines has increased in adolescent age groups with adolescent females reporting more misuse than males. Additionally, users often engage in polydrug use, involving opioids. Despite the prevalence of benzodiazepine use in adolescence, few preclinical studies have examined its ramifications on this age group. *Question:* Will diazepam (DZP) exposure during adolescence have a rewarding effect and will withdrawal potentiate anxiety-like behaviors? Additionally, will DZP exposure increase the behavioral response to morphine? Will these effects be sexually dimorphic? *Methods:* Adolescent male and female mice were group housed in one of three conditions,

diazepam (1, 2 mg/kg) and saline. Anxiety levels were measured using the elevated plus maze (EPM) before and after drug or vehicle exposure. A 14-day conditioned place preference (CPP) paradigm was used to examine the rewarding effects of DZP. To examine the effects of polydrug use with opioids, all mice were injected with 10 mg/kg morphine and locomotor behavior was recorded in an open field. All data were analyzed using two-way analysis of variance (ANOVA) with sex and dose as factors. *Results:* Our results suggest that DZP at both doses (1 & 2 mg/kg) produce a significant place preference in males, but not in females. However, withdrawal from DZP increased anxiety-like behaviors in both sexes. Furthermore, DZP exposure potentiates the response to morphine as shown in changes to locomotor behavior in both males and females. *Conclusion:* DZP induced withdrawal and potentiated the locomotor response to morphine in adolescent male and female mice. However, the rewarding properties of DZP are only seen in males. Little is known about benzodiazepine misuse in adolescence, with this study helping shed light on its potential consequences. These findings should be of interest to clinicians who prescribe benzodiazepines, as well as the broader scientific community.

Disclosures: D. Papasergia: None. **S. Bates:** None.

Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.05/SS18

Topic: G.09. Drugs of Abuse and Addiction

Support: R03DA045350 (FSH)
R03DA045833 (ITS)
U01DA054330 (ITS)

Title: The Lethal Toxicity of 3,4-Methylenedioxymethamphetamine (MDMA) and Methylone in Combination with Alcohol or Nicotine

Authors: *S. DRESSEL;
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Abstract: The Lethal Toxicity of 3,4-Methylenedioxymethamphetamine (MDMA) and Methylone in Combination with Alcohol or Nicotine Abdulrahman Ba Gunaid[1], Sydnee P. Dressel[1], Faith E Digby[2], Corey J. Widman[2], Alexander S. Wisner[2,3],Frederick E. Williams[1], Isaac T. Schiefer[2,3], F. Scott Hall[11]Department of Pharmacology and Experimental Therapeutics, [2]Department of Medicinal and Biological Chemistry, [3] Center for Drug Design and Development, College of Pharmacy and Pharmaceutical Sciences, The University of Toledo, Toledo, OH, USABackground: 3,4-methylenedioxy-methamphetamine (MDMA) and 3,4-methylenedioxy-N-methcathinone (methylone) are drugs that are commonly abused. These drugs are known for their psychoactive effects that result from increased synaptic levels of the monoamine neurotransmittersdopamine (DA), serotonin (5-hydroxytryptamine; 5-HT), and norepinephrine

(NE). MDMA and methylone are often taken with other substances like alcohol or nicotine in social scenes. These combinations may result in an increased toxicity and lethality. Methods: The lethal and toxic effects of MDMA and methylone were examined in combination with alcohol and nicotine as a model of drug overdose in 5-day post fertilization (dpf) larval zebrafish (*Danio rerio*). In each assay 6 zebrafish larvae were exposed to a drug or drug combination at multiple concentrations for 5 hours. Conclusion/Results:Lethal concentrations (LC50) for all drugs were determined. Combinations of MDMA and alcohol produced greater lethality than either alone, e.g., addition of the maximal non-lethal concentration(MNLC) of alcohol reduced the LC50 for MDMA, and addition of the MNLC of MDMA reduced the LC50 for alcohol. The addition of the MNLC of MDMA to nicotine also produced a small reduction in the LC50 value. However, when the MNLC of nicotine was added to MDMA, the LC50 value was *increased* (i.e., it was protective). The same pattern of effects was observed for methylone. Based on these results, when MDMA and methylone are combined with alcohol, greater lethality and toxicity occur than with either drug alone. However, the combination of MDMA and methylone with the MNLC of nicotine showed a promising reversal in lethality and toxicity. This may provide a rationale for developing a treatment for MDMA/methylone overdose, for which there are no current treatments aside from symptomatic relief.Supported by grants from the National Institute on Drug Abuse (USA): R03DA045350 (FSH),R03DA045833 (ITS), U01DA054330 (ITS)

Disclosures: S. Dressel: None.

Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.06/SS19

Topic: G.09. Drugs of Abuse and Addiction

Support: Papiit IA201622
Papiit IA202120

Title: Morphine self-administration alters brain structure and neuronal/glial density in male Wistar rats

Authors: *C. J. CARRANZA-AGUILAR, A. ELIZARRARAS-HERRERA, M. SERRANO-RAMIREZ, D. MEDINA-SÁNCHEZ, J. RASGADO-TOLEDO, D. ANGELES-VALDEZ, L. TRUJILLO-VILLARREAL, E. A. GARZA-VILLARREAL;
Inst. de Neurobiología, UNAM, Juriquilla, Mexico

Abstract: Introduction: Opioid use disorder involves compulsive use of opioids despite negative consequences. Studies have demonstrated that morphine produces changes in brain volume and glial activation, although the underlying mechanisms remain unclear. This study aimed to investigate the effect of morphine on drug-seeking behavior, brain volume, and neuronal/glial density in rats. Our hypothesis was that chronic morphine exposure would result in region-

specific alterations in brain structures characterized by distinct changes in cellular density. Methods: Male Wistar rats on Postnatal (P) day 35 underwent handling and habituation to operant chambers. Subsequently, a catheter connected to a non-magnetic access button was implanted in the Jugular vein. After a recovery period, two protocols involving active or inactive lever pressing for self-administration of morphine or saline (0.9%) infusions were conducted: 1) Morphine self-administration (0.01 mg/kg/infusion) under a Fixed Ratio 1 (FR1) schedule for 20 days, and 2) Morphine self-administration (0.1 mg/kg/infusion) using the same FR1 schedule, followed by a Progressive Ratio 9-4 (PR) schedule for 20 days. To assess structural changes in the brain, in vivo 3D magnetic resonance imaging (MRI) scans (sequence: TR = 30.76 ms, TE = 5 ms, rotation angle = 10°, slice thickness = 25.6 mm, FOV = 28.2 x 19 x 25.6 mm, and isometric voxel size = 160 µm) were performed before treatment and during FR1 and PR schedules. Immunofluorescence staining of microglia (anti-Iba1) and neurons (anti-NeuN) was conducted after each protocol. Results: We observed a gradual increase in morphine infusions during the FR1 schedule that stabilized during the PR schedule. Furthermore, the morphine group exhibited a progressive increase in active lever pressing, while inactive lever pressing remained stable and similar to the control group. MRI scans showed that morphine led to decreased volume in six brain regions, including the insular cortex ($p = 0.043$), while 14 regions, including the brainstem ($p = 0.045$), exhibited increased volume. In comparison to the control group, morphine self-administration increased the population of microglial cells in the brainstem, while the number of neurons remained unchanged. Similarly, in the insular cortex, there was an increase in microglial cell count, but a decrease in neuronal cell count. Conclusion: The changes in brain volume induced by morphine are related to alterations in neuronal populations and influenced by neuroinflammation, indicating a potential association between cellular changes and macrostructural modifications.

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Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.07/SS20

Topic: G.09. Drugs of Abuse and Addiction

Title: Adolescent Social Isolation Increases Vulnerability to Voluntary Opioid Consumption in Adulthood in Rats

Authors: *P. LEMEN, H. CHEN, J. HUANG;
Integrated Biomed. Sci. - Genetics, Genomics, Informatics, Univ. of Tennessee, Memphis, TN

Abstract: Social stress during adolescence can cause behavioral changes lasting into adulthood and is a risk-factor for substance use disorder, but the effect varies between individuals. This

study characterizes how social isolation in adolescence affects opioid use and anxiety-like behavior in adulthood using the inbred strains WKY and DSS rats. We compare adulthood oxycodone intake in self-administration and behavior in an elevated plus maze (EPM) between rats either group housed (GH) or isolated for 6 weeks during adolescence. We also develop a method (PeerPub) for operant oral intake of two rats in the same chamber to better model human social condition. Our data shows rats isolated during adolescence (n = 12/group) have higher vulnerability to oxycodone consumption in adulthood (WKY females P=0.006, WKY males P=0.01, DSS females P=0.02, DSS males P=0.05). We also found differences in anxiety-like behavior between experimental phases (baseline, post-drug, and withdrawal). Overall, our data indicates that rats isolated during adolescence have less anxiety-like behavior before oxycodone exposure, a decreased sensitivity to the negative effects of oxycodone, however, they consume more drug. These data demonstrate a need for better understanding in the role social environments play in vulnerability to drug use. We plan to examine underlying molecular mechanisms associated with these phenotypes in future studies.

Disclosures: **P. Lemen:** None. **H. Chen:** None. **J. Huang:** None.

Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.08/SS21

Topic: G.09. Drugs of Abuse and Addiction

Support: MFDS of the Republic of Korea Grant 22214MFDS251

Title: Flualprazolam, a designer benzodiazepine, induces psychological and physical dependence in rodents

Authors: *D. KIM, Y. LEE, W.-A. KOOK, A. DONIO, H.-W. MIN, S.-B. HWANG, S.-Y. LEE, C.-G. JANG;
Sungkwunkwan Univ., Gyeonggi-do/Suwon, Korea, Republic of

Abstract: Flualprazolam is a designer drug to clandestinely circumvent government regulations. It can be purchased via internet easily. Thus, it is generally abused for its sedative/hypnotic effects by young adults for recreation. Flualprazolam is structurally related to the triazolobenzodiazepine, producing central nervous system (CNS) depression. Although flualprazolam is structurally similar to alprazolam, a single fluorine atom of it increases pharmacokinetic parameters including half-life and volume of distribution leading to a potential for greater toxicity and drug addiction than alprazolam. For strict vigilance and to make regulations for this drug, we must know the effect of flualprazolam including psychological and physical dependence. So, we planned to estimate the drug effect using C57BL/6J mice(7~8weeks) at locomotor activity test and withdrawal (WD) test to confirm effect on baseline locomotor activity and physical dependence. Sprague Dawley (SD) rats (4weeks) were

used for intravenous self-administration (IVSA) to investigate flualprazolam induced psychological dependence. In locomotor activity test, five dose of flualprazolam, 0.03, 0.1, 0.3, 1 and 3 mg/kg significantly reduced spontaneous locomotor activity in C57BL/6J mice (n=9). Continually, we injected flualprazolam intraperitoneally during 7days. 24 hours after the last flualprazolam injection, we observed the withdrawal symptoms. We confirmed that treatment with flualprazolam at 0.6mg/kg dose induced physical dependence, especially high forepaw tremor (n=9). In IVSA, two dose of flualprazolam, 0.01 and 0.03mg/kg per infusion significantly increased the number of infusions and active lever pressing compared to vehicle (n=6). All data were analyzed using ANOVA with Fisher's LSD post hoc test. The findings of this study demonstrate that flualprazolam has reinforcing effect and dependence in rodent models.

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Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.09/SS22

Topic: G.09. Drugs of Abuse and Addiction

Support: ICTI-PICIR-075
CIC-UMSNH 16125
CIC-UMSNH 16124
CIC-UMSNH 16060

Title: Chronic toluene exposure and diabetes increases vascular adrenergic effects in rats

Authors: L. TAPIA-HERNANDEZ[1], D. GODINEZ-HERNANDEZ[2], L. F. ORTEGA-VARELA[3], *M. Y. GAUTHEREAU-TORRES[1];
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Abstract: Recreational use of inhalants, like toluene, is a serious drug abuse problem all over the world, mainly affecting children and teenagers. Toluene shares pharmacological properties with central nervous system depressants, and it is commonly inhaled to achieve intoxicating states. It can be found in products like thinner, spray paint and glue. Toluene can cause cardiovascular damage, arrhythmias and sudden sniffing death probably due to adrenergic sensitization of the heart. On the other hand, diabetes is one of the main chronic diseases with a high incidence and death. It is known that diabetes can generate serious health problems such as cardiovascular damage, lowering quality of life. Adrenergic receptors are present in different amounts in tissues, including brain, heart and blood vessels. The main functions of these receptors include modulation of neurotransmission, regulation of metabolism, inotropy, chronotropy, and

vasoconstriction. The purpose of this study was to investigate if chronic toluene exposure modifies alpha-1 adrenergic responses in aorta of diabetic rats. 4 groups of Male Wistar rats (8-9 weeks) were placed in static exposure chambers during 30 minutes, twice a day, during 4 weeks. Group 1 was a control group exposed to air; group 2 was induced to diabetes (50 mg/dl of streptozotocin) and exposed to air; group 3 was exposed to 6000 ppm of toluene and group 4 was induced to diabetes and exposed to 6000 ppm of toluene. After this period, rats were euthanized with sodium pentobarbital (65 mg/kg) and aorta was isolated, it was cut into rings and the endothelium was removed from half of them. Arterial rings were bathed in a 10 ml chamber, filled with Krebs-Henseleit solution, and attached to the bottom of the chamber and to an isometric force displacement transducer. Aortic rings were subjected to an initial optimal tension of 3 g and were stimulated with a submaximal concentration of phenylephrine ($1x10^{-7}$ M). Concentration-response curves to phenylephrine (alpha-1 adrenergic agonist: $1x10^{-9}$ - $1x10^{-5}$ M) were made. Our results showed that phenylephrine produced a contraction in a concentration-dependent manner in all groups, and that chronic toluene exposure in aortic rings with endothelium from diabetic rats produced a higher response to phenylephrine compared with the other groups. In addition, in endothelium-denuded rings, chronic toluene exposure generated a greater response to phenylephrine compared with control, diabetes and toluene-diabetes groups. In conclusion, our findings suggest that chronic toluene exposure in diabetic and non-diabetic rats increases alpha adrenergic responses probably due to an endothelium-dependent mechanism.

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Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.10/SS23

Topic: G.09. Drugs of Abuse and Addiction

Support: Grant-in-Aid for Scientific Research(C) 20K10549

Title: Evaluation of the effects on the dopaminergic reward system and the blood-brain barrier permeability of diphenidine derivatives using rat brain microdialysis

Authors: *Y. TAKAHASHI[1,2], K. OKUDA[1], M. ASARI[1], K. MORI[1], R. NAMBA[1], W. OCHIAI[2], K. SHIMIZU[1];
[1]Asahikawa Med. Univ., Asahikawa City / Hokkaido, Japan; [2]Hoshi University, Grad. Sch. of Pharmaceut. Sci., Shinagawa-Ku / Tokyo, Japan

Abstract: Background: Diphenidine (DPD) - a new psychoactive substance - has a chemical structure similar to phencyclidine and ketamine. DPD and some of its derivatives are designated as controlled drugs in Japan and many other countries. Recently, we have reported that brain dopamine contents are increased after intraperitoneal (i.p.) administration of DPD and its

derivatives (4-methoxy-DPD and 4-hydroxy-DPD): brain concentrations tend to peak at 30 to 45 min after administration, and then gradually decrease in a time-dependent manner. These results demonstrated that the DPD derivatives could penetrate the blood-brain barrier (BBB). In this study we evaluated the neurochemical effects on the dopaminergic reward system and the BBB permeability of i.p. injected 4-methoxy-DPD and 4-hydroxy-DPD using rat brain microdialysis.
Methods: Male Slc:Wistar/ST rats were anesthetized and stereotaxically implanted with a microdialysis probe in the right nucleus accumbens (NAc, A: +2.0 mm; L: +1.5 mm from the Bregma; V: -6.0 mm from the skull). Perfusion was performed the following day. An inhibitor of various transporters expressed in the BBB was injected subcutaneously 1 hr before i.p. injection of 4-methoxy-DPD or 4-hydroxy-DPD at 20 mg/kg. Dialysates were collected and then analyzed by HPLC-ECD for the dopamine content and by LC-MS/MS for determination of DPD derivatives.
Results and Discussion: The 4-methoxy-DPD and dopamine contents in the rat-brain dialysate were significantly increased with pretreatment of P-glycoprotein inhibitors, verapamil, and quinidine compared to vehicle control. Conversely, the 4-hydroxy-DPD and dopamine contents in the dialysate were significantly decreased with pretreatment of an organic cation transporter inhibitor, diphenhydramine. The peak concentration of 4-hydroxy-DPD in the dialysate was higher than that of 4-methoxy-DPD. This effect of 4-hydroxy-DPD on the dopaminergic reward system was consistently observed: i.e. levels were always higher compared to DPD and 4-methoxy-DPD. These findings suggest that the efflux transporter P-glycoprotein limits the BBB permeability of 4-methoxy-DPD, and the influx transporter organic cation transporter is involved in the potent BBB permeability of 4-hydroxy-DPD. We conclude that it was important to consider the pharmacokinetics, such as the BBB permeability and behavior of the metabolites, when evaluating the effects of novel psychoactive substances.

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Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.11/SS24

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R03DA045350 (FSH)
NIH Grant R03DA045833 (ITS)
NIH Grant U01DA054330 (ITS)

Title: High ambient temperatures potentiate the lethality of MDMA and MDMA-like synthetic psychoactive cathinones in larval zebrafish

Authors: *L. KOUNTZ;
Univ. of Toledo, Toledo, OH

Abstract: High ambient temperatures potentiate the lethality of MDMA and MDMA-like synthetic psychoactive cathinones in larval zebrafish

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In recent years, there has been an increase in the number, potency and availability of novel psychoactive drugs that duplicate the effects of many well-established illicit drugs. Between 2005 and 2011, the European Monitoring Centre for Drugs and Addiction (EMCDDA) Early Warning System identified 164 new psychoactive substances in the EU (Bretteville-Jensen, 2013). Many of these are derivatives of cathinone, the naturally occurring β-ketone analogue of amphetamine found in *Khat (Catha edulis)* that produce amphetamine-like sympathomimetic effects (Valente, 2014). These effects include tachycardia and hypertension, as well as some psychoactive effects such as euphoria and increased alertness. There have been some synthetic psychoactive cathinones (SPCs) derived that mimic methylenedioxymethamphetamine (MDMA) and cocaine as well, and have come into wide illicit use. Many individuals take these drugs unknowingly, thinking they are other drugs, as shown in a study of individuals that thought they were consuming MDMA (Palamar, 2016). The majority of these individuals have consumed SPCs, including methylone, dimethylone, α-pyrrolidinovalerophenone, and others. SPCs are often taken at parties or clubs. The lethal and toxic effects of MDMA and methamphetamine are exacerbated by elevated ambient temperatures (Cappon, 1997), and this has been shown in mice (Chen, 2021). As a higher throughput approach to evaluating SPC toxicity, the Hall laboratory has been using larval zebrafish. It is not known whether higher ambient temperatures exacerbate lethal toxicity in larval zebrafish. This question was addressed in experiments examining MDMA, and a series of structurally similar MDMA-like SPCs. Firstly, these studies showed that high ambient temperatures exacerbate MDMA toxicity in larval zebrafish. Moreover, the same was observed for all SPCs. There was some variability in the magnitude of this effect which may be used to identify structure activity relationships as a wider range of analogues are studied.
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Disclosures: L. Kountz: 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 Institute on Drug Abuse (USA): R03DA045350 (FSH), R03DA045833 (ITS), U01DA054330 (ITS).

Poster

PSTR297. Addictive Drugs: Drug Tolerance, Dependence, and Toxicity

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR297.12/SS25

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA047717

Title: Characterization of spontaneous withdrawal following continuous fentanyl administration in female and male rats

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Abstract: Fentanyl, a high potency synthetic opioid, is the leading cause of drug overdose in the United States. The widespread use of fentanyl suggests that dependence develops rapidly and withdrawal symptoms are severe. This hypothesis was tested by examining withdrawal symptoms in female and male Sprague-Dawley rats receiving continuous fentanyl administration for 3 days. Given that opioid administration to treat pain can be a gateway to opioid dependence, rats were injected with CFA into the right hindpaw to induce persistent inflammatory pain. The side effects of fentanyl (1 mg/kg/day) administration almost completely depressed home cage wheel running during the first day of administration. Running in male rats recovered to CFA levels on Days 2 and 3, whereas running in female rats remained depressed for all 3 days. Abrupt termination of fentanyl administration induced withdrawal as measured by depression of wheel running, a decrease in body weight, and an increase in wet dog shakes. Both male and female rats lost approximately 10% of their body weight in the 24 hrs following termination of fentanyl administration. An equally quick decrease in wheel running and increase in wet dog shakes occurred in female rats undergoing withdrawal. Depression of wheel running and increased wet dog shakes was delayed until the second day of fentanyl withdrawal in male rats. Withdrawal symptoms persisted for at least 4 days in female and male rats. These data demonstrate that fentanyl dependence develops rapidly with continuous administration and withdrawal symptoms are more severe in female compared to male rats.

Disclosures: M.M. Morgan: None. **K. Ataras:** None.

Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR298.01/TT1

Topic: H.03. Decision Making

Support: Office of Naval Research (Global)
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National Health and Medical Research Council (NHMRC) Ideas grant.
APP2010899

Title: A functional network for evidence accumulation during perceptual decision-making revealed with model-based fMRI

Authors: *J. WONGTRAKUN, S.-H. ZHOU, M. A. BELLGROVE, T. T. J. CHONG, J. P. COXON;
Turner Inst. for Brain and Mental Hlth., Monash Univ., Melbourne, Australia

Abstract: Accumulating sensory information to inform a decision is a noisy process that occurs in close temporal proximity to attentional selection and motor planning and execution. Consequently, elucidating which networks encode the different stages of a perceptual decision with fMRI has proven challenging. Here, we employed a custom random dot-motion paradigm, alongside a conjunction analysis, in a sample of 50 healthy adults (27 females; age mean ± standard deviation, 25 ± 5.98 years) with the aim of reducing the impact of attention and motor-related processes on evidence accumulation, i.e., the act of gathering sensory information towards a decision, during perceptual decision-making. We show that BOLD activity increases during perceptual decisions concerning changes in visual motion across a bilateral frontoparietal network consisting of the intraparietal sulci, anterior insula, and premotor and pre-supplementary motor areas. Additionally, activations in the caudate and putamen suggest the basal ganglia plays an active role when gathering sensory evidence. We applied drift diffusion modelling to the behavioural data and parametrically modulated BOLD activation within this network by the modelled parameters of drift rate, decision threshold, and non-decision time. We observed that slower drift rates (prolonged evidence accumulation) and greater non-decision time values corresponded with increased BOLD activity within this network. In contrast, BOLD activity was not parametrically modulated by the decision threshold parameter. Overall, through novel experimental design and analysis procedures, these findings clarify brain regions thought to be involved in the evidence accumulation, but not attentional selection or motor execution, stage of perceptual decision-making in humans.

Disclosures: J. Wongtrakun: None. **S. Zhou:** None. **M.A. Bellgrove:** None. **T.T.J. Chong:** None. **J.P. Coxon:** None.

Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR298.02/TT2

Topic: H.03. Decision Making

Support: JSPS KAKENHI (20H00123)

Title: Unveiling the Mechanism of Temporal Scaling in Neural Representations in a multiple-timescale model

Authors: *T. KURIKAWA;
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Abstract: Unveiling the Mechanism of Temporal Scaling in Neural Representations in a multiple-timescale model

Understanding how temporal information is encoded in the neural system is pivotal for comprehending various cognitive functions, including working memory tasks. Recent experimental studies have demonstrated that neural states exhibit varying speeds depending on contextual factors, while maintaining highly similar trajectories—an intriguing phenomenon known as temporal scaling. Theoretical investigations have utilized reverse engineering methods to analyze this temporal scaling of neural representations. However, the underlying mechanism remains elusive, with the process often described as a black box.
In our previous study (Kurikawa and Kaneko, 2021, Frontiers in Computational Neuroscience), we developed a multiple-timescale neural network capable of generating robust sequential patterns for performing working memory tasks (Kurikawa, the proceedings of ICANN 2021). This network model is constructed using a simple learning rule that adheres to the principle of locality, requiring only pre- and post-synaptic information. As a result, the structure of the neural dynamical systems following learning becomes transparent. In the present study, we employed this model to elucidate the mechanism underlying temporal scaling in neural representations across different contexts.
By training the network to generate sequences under specific contexts, represented by distinct input strengths of the external input and varying gain parameters of the activation function in the neurons, we observed the emergence of temporal scaling. We discovered that neural trajectories are composed of pseudo fixed-point attractors, and the stability of these attractors is simultaneously modulated by the strength of the external input and/or the gain parameter. The regulated stability of these attractors leads to transitions of neural states from one attractor to another at different speeds, contingent upon the input strength and/or the gain parameter. Additionally, we identified a network structure that enables global regulation of attractor stability. Collectively, our findings propose a novel mechanism underlying temporal scaling in the neural system.

Disclosures: **T. Kurikawa:** None.

Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

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Topic: H.03. Decision Making

Support: NIH Grant R01DA048096 (KTK)
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NIH Grant R01MH124115 (KTK)

Title: Feature-level uncertainty, estimated via temporal difference reward prediction errors, may describe a mechanism underlying paradoxical learning phenomenon.

Authors: *A. R. SHIPP, K. KISHIDA;
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Abstract: Computational reinforcement learning theory has a well-established role in investigating value-based decision-making and learning in computational and biological agents. It has been used to consider other decisions, like implicit choices expressed as 'selective attention' (Dayan, et al., 2000). In contrast to considering selective attention as a resource constraint problem, Dayan and colleagues proposed a novel approach that viewed attention as an optimal learning problem. Their approach requires prior knowledge of the statistical variance of various features' reward predictability. This can work extremely well for computer agents where such knowledge may be provided; however, biological agents require a way to estimate this variance in a constantly evolving environment. We hypothesize that phasic dopamine levels, generated in response to temporal-difference reward prediction errors (TD-RPEs), can provide not only a learning signal for reward-value updating, but also direct estimates of associated uncertainty (i.e., information levels).
Our approach largely follows Dayan and colleagues' framework, but instead of requiring prior knowledge of statistical variance, we hypothesize that the standard deviation may be directly conveyed by TD-RPEs (and thereby phasic dopamine levels in mammals, including humans). From this signal, we show how uncertainty may modulate estimates of feature precision, reliability, and learning rates. Specifically, TD-RPE's can provide the quantitative signal required to adjust learning rates and differentially weight the expected values of predictive features. Our model provides a hypothetical mechanism for selective attention through precision-weighting of features and value-based choice. It also provides a hypothetical mechanism for how mammalian brains may estimate feature-level uncertainty. We explored whether our model may explain other learning phenomenon that appear paradoxical within traditional reinforcement learning. We ran simulations of various tasks and found that our model may explain Kamin blocking, latent inhibition, extinction and renewal, one-shot learning, and saliency of novel stimuli. Future work will compare our model to human behavioral data and sub-second dopamine fluctuations to test the hypothesis that dopamine levels augment behavior in a manner consistent with signaling of feature-level uncertainty via TD-RPEs.

Disclosures: **A.R. Shipp:** A. Employment/Salary (full or part-time):; Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA, Neuroscience Graduate Program, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA. **K. Kishida:** A. Employment/Salary (full or part-time):; Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA, Neuroscience Graduate Program, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA, Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC 27101, USA.

Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR298.04/TT4

Topic: H.03. Decision Making

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Grant OPUS 2019/35/B/NZ7/03477 from the National Science Centre Poland
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Title: Statistical framework for identification of individual and social aspects of animal learning in Intellicages

Authors: B. JURA[1], M. LENARCZYK[1], Z. HARDA[2], L. SZUMIEC[2], M. ZIEMIAńSKA[2], J. RODRIGUEZ PARKITNA[2], ***D. K. WOJCIK**[3,1];
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Abstract: Several recent cage designs support studies of multiple animals housed for weeks with minimal human intervention in a single or multiple compartments where they can interact with cage elements and with each other, and their behavior can be tracked in various ways. Here we focus on Intellicage system where up to 14 female mice housed together can be identified with an RFID transponder interacting with intelligent corners providing reward, and the behavior is described in terms of discrete events. We present a general conceptual, analytical and computational framework for stochastic description, analysis and modeling of data from such cages. This framework combines the theory of point processes (as used in spike train analysis) with reinforcement learning models. We demonstrate how individual and social aspects of learning can be identified within the data, and show different specific approaches which facilitate study of effects of the whole group on an animal or formation of a hierarchy of social effects in group learning. The results of the analysis are validated with equivalent simulated data.
To illustrate this conceptual framework and our analytical approach we designed an experimental paradigm where rewards are offered depending on an arbitrary assignment of an animal to one of two groups, “majority” or “minority”. The two groups were assigned different locations with reward availability, changing in consecutive phases of the experiment. We show that the data support importance of the social effects in animal learning of the reward and may also be used to identify a social structure within the group. Corresponding generative models can be used for validation of various analytical methods and for prediction of mice behavior.

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Poster

PSTR298. Computational Models for Decision-Making

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Topic: H.03. Decision Making

Support: DFG JA 1999/3-1
ERC StG MEMCIRCUIT 758032

Title: Striatal dopamine teaching signals reflect an agent's perceived locus of control

Authors: *T. BERNKLAU, B. RIGHETTI, L. S. MEHRKE, S. N. JACOB;
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Abstract: Striatal dopamine drives associative learning by acting as a teaching signal. Much work has focused on simple learning paradigms, in which dopaminergic signals passively track the statistics of externally controlled outcomes. However, higher cognition requires an agent to generate internal concepts of its environment, in which sensory stimuli, actions, and outcomes become associated. To address the role of dopamine in this learning process, we performed direct dopamine measurements across the striatum and computational modeling in mice learning cue-instructed actions following implicit task rules. We found that cue-triggered and outcome-triggered dopamine signals were not consistently coupled through an inverse relationship as in Pavlovian learning, but depended on the adopted behavioral response strategy. When animals applied simple behavioral strategies that did not incorporate mechanistic links between cues, actions, and outcomes, passive reward predictions were reflected in distinct cue dopamine signals for trials in which animals expected higher or lower returns. As the animals rediscovered the impact of their own actions, dopaminergic reward predictions for the different trial events were recoupled, indicating a crystalizing understanding of the current task. Temporal-difference reinforcement learning models reproduced the main behavioral and dopaminergic signatures. We incorporated mechanistic hypotheses derived from our experimental findings into the models' architectures and found that reward prediction errors (RPEs) in the form of state-action value prediction errors approximated the observed dopamine signals well. Modeling suggested an adjustment in the animals' learned cue-action-outcome associations after rule switches. The experimental data showed that outcome dopamine signals re-emerged upon introduction of a new task rule and did so equally across different conditions despite strong differences in behavioral performance, which should have triggered different RPEs. This disruption after rule switches could be modeled by a reset of state-action values that was only partial and discarded outcome-predictive information but retained choice-guiding information, indicating that the learned cue-action-outcome association had been cut. Off-policy and on-policy learning predicted qualitatively different RPE signatures after rule switch. Our dopamine data clearly favored the on-policy variant, matching the deterministic nature of our task that did not encourage exploration. Together, our experimental and modeling results suggest that dopaminergic RPEs reflect an agent's perceived locus of control.

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Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.06/TT6

Topic: H.03. Decision Making

Support: 1U19NS118246

Title: Disentangling self- and object-motion in a target interception task: normative strategies and neural circuits

Authors: *J. VASTOLA[1], V. VENCATO[2], J.-P. NOEL[2], G. C. DEANGELIS[3], D. E. ANGELAKI[2], J. DRUGOWITSCH[1];
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Abstract: Whether motion across the retina is due to object motion, self-motion, or a mix of both is often ambiguous. Resolving this ambiguity is important, since animals may have to react differently depending on whether, e.g., a predator is moving towards them or not. We study the required disentangling of self- and object-motion, a form of dynamic causal inference, in the context of a novel navigation task for both humans and macaque monkeys. In each trial, subjects in a virtual reality environment first briefly observe a target that may or may not be moving, and they may also experience self-motion. After that, the target becomes invisible and subjects must attempt to intercept it by using a joystick to steer through the virtual environment. We find that the behavior of humans (N = 5 naïve, 2 non-naïve) and a monkey (N = 1) is consistent with the predictions of a normative model which couples (i) a Bayesian strategy for target trajectory inference with (ii) near-optimal navigation that minimizes a certain set of costs (including movement costs and proximity-to-target costs). In particular, major qualitative features of the behavioral data (like a biased assessment of target motion given self-motion) are consistent with the model, and quantitative features like subjects' trajectories can be fit reasonably well. Given that the model appears to describe behavioral data well, we also construct a biologically plausible neural circuit model that suggests how our proposed strategy might be implemented by the brain. The circuit model, which couples several probabilistic population codes, is consistent with ideas about how causal inference may be reflected in the cortical hierarchy: primary sensory cortices reflect estimates according to each possible causal structure, which are then combined in intermediate areas (e.g., posterior parietal cortex), and used to drive decisions in downstream areas.

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Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR298.07/TT7

Topic: H.03. Decision Making

Title: Impulsive decision-making and indicators of psychoemotional and cardiovascular health in a cohort of Medical Students

Authors: *S. GUARDO[1,3], A. F. SARMIENTO[3], M. GAVIRIA[3], E. LADINO[3], G. TOVAR[3], G. D. BRICEÑO[4], J. A. CESPEDES[3,5], S. LOPEZ-GUZMAN[2];
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Abstract: Depression and anxiety in medical students are known to be linked to psycho-emotional and social factors. High academic demands and stress can lead to unhealthy choices in lifestyle that range from lack of exercise, poor nutrition, all the way to alcohol and drug use. These unhealthy behaviors can have lasting consequences on mental and cardiovascular health that could persist into their professional work life and potentially impact patient care. The link between stress and unhealthy habits is not fully understood and has been understudied in this population, but other studies have pointed to maladaptive decision-making as candidate mechanism. This type of decision-making, also known as choice impulsivity, refers to the tendency to prefer immediate rewards over better long-term rewards, and is known to be increased in individuals with substance use disorders, and in people with obesity. In college students, choice impulsivity is associated with lower academic performance, greater alcohol use, and a lower age for starting smoking and risk of obesity. In this study we explore the relationship between stress, impulsive decision-making, and poor health in a cohort of medical students in Colombia.**Materials and Methods:** Cross-sectional observational study (n = 176 students) of first-year medical students at a university in Bogota, Colombia (ages 17-19). We obtained baseline measures of cardiovascular health (CVH), nutrition, body mass index (BMI), perceived stress, self-reported empathy, self-reported emotional intelligence, and choice impulsivity in the first months after starting the program. Choice impulsivity was assessed through a computerized delay discounting task, where students had to choose between immediate and delayed monetary rewards. A computational model was applied to each individual dataset to derive subject-specific parameters, the discount rate (DR) that indexes the level of choice impulsivity.**Results:** Preliminary results did not indicate a significant correlation between DR and CVH. However, a specific relationship was found between BMI and DR. Regarding the relationship with psycho-emotional factors, DR was proportionally related to the level of perceived stress, and it was inversely proportional to the level of empathy.**Conclusions:** Data collection and analyses are still ongoing, but these preliminary results indicate that choice impulsivity may be an indicator of poor lifestyle in medical students and it may reflect high levels of stress. Psycho-emotional compensatory mechanisms such as empathy and emotional intelligence may be important coping tools for minimizing the impact of stress on decision-making and lifestyle.

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Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR298.08/TT8

Topic: H.03. Decision Making

Title: Cognitive model discovery via disentangled RNNs

Authors: *K. MILLER, M. ECKSTEIN, M. BOTVINICK, Z. KURTH-NELSON;
Google DeepMind, London, United Kingdom

Abstract: Computational cognitive models are a fundamental tool in behavioral neuroscience. They instantiate in software precise hypotheses about the cognitive mechanisms underlying a particular behavior. Constructing these models is typically a difficult iterative process that requires both inspiration from the literature and the creativity of an individual researcher. Here, we adopt an alternative approach to learn parsimonious cognitive models directly from data. We fit behavior data using a recurrent neural network that is penalized for carrying information forward in time, leading to sparse, interpretable representations and dynamics. When fitting synthetic behavioral data from known cognitive models, our method recovers the underlying form of those models. When fit to laboratory data from rats performing a reward learning task, our method recovers simple and interpretable models that make testable predictions about neural mechanisms.

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Poster

PSTR298. Computational Models for Decision-Making

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Topic: H.03. Decision Making

Support: National Key R&D Program of China (No. 2021YFA1101804)
National Science and Technology Innovation 2030 Major Program (No. 2021ZD0203700 / 2021ZD0203704)

Title: Marmosets accumulate dynamic sensory evidence for decision-making

Authors: *X. XIA, N.-L. XU;
Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China

Abstract: Dynamic evidence accumulation is an important cognitive process, in which the brain accumulates the dynamically unfolding sensory evidence for discriminating the complex stimulus. The dynamic evidence accumulation task recently has been used in rodents to research

the neural mechanisms of perceptual decision-making, while only a few studies in non-human primates. Marmoset is a promising non-human primate model in cognitive neuroscience, however, the cognitive task training in marmoset still is a main technical bottleneck, which has limited its application in cognitive neuroscience. In here, we established a head-fixed marmoset behavior training protocol, and we trained the marmoset to learn an auditory-based dynamic evidence accumulation task. During the task training, there are three nozzles in front of the head-fixed marmoset. For each trial, the marmoset initiates the task by licking the central nozzle, after which the auditory stimulus is delivered, and the marmoset reports its decision by licking the left or right nozzle to get the reward. With this training paradigm, we established an evidence accumulation task in marmosets. In this task, the auditory stimulus is a pure tone sequence which consists of low frequency (5.4KHz) and high frequency(11.8KHz). There are 5 tones in each stimulus and the tone duration and tone interval both are 125ms. The marmoset needs to adjudicate whether there are more high-frequency or low-frequency tones. If the low-frequency tones are more, the marmoset should lick left nozzle and vice versa. During the auditory stimulus playing, the marmoset is not allowed to response until a go cue to inform marmoset to response. We found that the marmoset can learn this task with about 80% accuracy. For this task, another possible task strategy is random selection strategy, in which the animals randomly select one tone to make decision, this strategy does not require evidence accumulation. we built a behavior model based on random selection strategy and compared the behavior performance between the marmoset and model. We found that the difficult trial accuracy of marmoset is higher than the model. This result suggests that the marmoset indeed accumulates the evidence to make decision. Given the marmosets are easier to increase training throughput and use various circuit analysis tools comparing with rhesus monkey, our work paves the way for uncovering the neural circuit mechanisms of auditory evidence accumulation in non-human primates.

Disclosures: **X. Xia:** None. **N. Xu:** None.

Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR298.10/TT10

Topic: H.03. Decision Making

Support: NSF Award 2146888

Title: Humans are excessively indecisive under time constraints

Authors: *S. R. SULLIVAN[1], R. LOKESH[1], J. A. CALALO[1], A. ROTH[1], C. S. PETERS[1], J. H. BUGGELN[1], T. T. NGO[1], M. J. CARTER[2], J. CASHABACK[1];
[1]Univ. of Delaware, Newark, DE; [2]McMaster Universtiy, Hamilton, ON, Canada

Abstract: Failing to decide on a movement when acting under time constraints can be detrimental, such as a driver who fails to decide where to steer a car and causes a crash. Research

in decision-making has explored how humans select motor plans to maximize reward given the inherent sensorimotor delays and uncertainties. Yet studies imposing time constraints have not examined indecisive behaviour, where humans fail to decide before a deadline. Here we test the idea that optimal motor planning that accounts for sensorimotor delays and uncertainties will result in indecisions.To investigate, participants grasped the handle of a robotic manipulandum. A screen displayed a start position and two potential targets. The right and left targets were 20 cm forward of the start position. The participant hand position and a computer agent were displayed with separate cursors. Participants received one point if they reached the same target as the agent, zero points if they reached the opposite target, or zero points if they were indecisive and failed to reach a target by 1500 ms. The participant and agent began each trial in the start position. The agent cursor moved directly from the start position to either the right or left target. Movement onset of the agent was drawn from a normal distribution, with the mean and standard deviation fixed within a condition. Between conditions we manipulated the mean and standard deviation of the movement onset of the agent using a 3 (mean: 1000, 1100, 1200 ms) x 2 (standard deviation: 50, 150 ms) repeated measures design. We developed a model that finds the optimal time to either react to the agent or guess a target to maximize expected reward. Inputs to the model include the delays and uncertainties associated with reaction time, movement time, coincidence timing, and the agent movement onset. Based on the optimal timing for each experimental condition, the model can also predict the percentage of trials that should result in indecisions. The model predicts more indecisions in the 1100 ms conditions than the 1000 ms conditions, and less indecisions in the 1200 ms conditions than the 1000 ms conditions. Aligning with the model, we found that participants made more indecisions in the 1100 ms compared to the 1000 ms conditions ($p < 0.001$). However, participants made more indecisions in the 1200 ms condition than the 1000 ms condition ($p = 0.004$), which was the opposite trend predicted by the model. Critically, on average the participants made 19% more indecisions in the 1200 ms condition relative to the model. Taken together, our results suggest that humans suboptimally account for sensorimotor and temporal uncertainties, leading to an excessive number of indecisions.

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Poster

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Topic: H.03. Decision Making

Title: Is metacognitive ability conserved across perceptual and value-based decision-making?

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Abstract: Objective: Metacognition is the process of reflecting on one's own thoughts and decisions. Metacognitive ability refers to the accuracy with which confidence reports capture decision quality. Typically, metacognitive ability is measured through modeling the relationship between confidence reports and behavior in decision-making tasks where each trial has an objectively correct answer. As a result, studies of the generalization of metacognitive ability across different cognitive domains have mostly been limited to tasks where decision accuracy can be assessed, such as perceptual decision-making and memory. A relatively unexplored domain is value-based decision-making, where tasks probe preference rather than performance based. However, computational models of value-based choice allow for an analysis of preference behavior akin to that of perceptual decision-making, rooted on the assumption of a probabilistic choice process that is a function of signal strength, in this case, subjective value superiority. Here, we leveraged this computational approach and addressed the question of domain generality by comparing metacognitive ability across three different decision-making tasks spanning perception and value. Methods: Online participants enrolled through CloudResearch completed three computerized decision-making tasks (an orientation discrimination task, a delay discounting task, and a risk/ambiguity preference task) with trial-by-trial confidence reports. The orientation discrimination task was composed of two high-complexity blocks (oriented gratings presented at 5-6 different levels of contrast) and two low-complexity blocks (1-2 levels of contrast). Confidence reports from all three tasks were fit with the CASANDRE model which interprets confidence as an estimate of decision reliability (not of the probability of a decision being correct) and captures metacognitive ability with a single parameter, "meta-uncertainty", expressing the precision of uncertainty representation (Boundy-Singer, et al., 2023). Results: Preliminary results confirm a strong correlation of metacognitive ability within the perceptual domain, when comparing meta-uncertainty derived from the high-complexity versus low-complexity blocks. Similarly, our results show meta-uncertainty correlated across the two value-based decision tasks. Interestingly, we found that meta-uncertainty from the perceptual task was also related to meta-uncertainty from the value-based task, suggesting that metacognitive ability may be domain-general across confidence in both performance and preference.

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Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR298.12/TT12

Topic: H.03. Decision Making

Support: Pathway Programme Grant from Science Foundation Ireland (21/PATH-S/9643)
Wellcome Trust Investigator Award (219572/Z/19/Z)

Title: A Hierarchical Model of Decision-making Fit to Simulated Behavioural and Neural Decision Signal Data using a Single trial Joint Likelihood

Authors: *J. EGAN, S. KELLY, E. CORBETT;
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Abstract: Recent research has demonstrated benefits in using human EEG signatures of decision formation alongside behavioral data to construct and fit models of perceptual decision-making that reflect the brain's decision algorithms. However, while neurally-informed models have been fit using grand-average neural data, or to neural data from specific individuals separately, neurally-informed models have yet to be fit using a hierarchical design that combines group and individual data. Here, using simulated 'ground-truth' data, we demonstrate a neurally-informed hierarchical modelling approach that uses simulation and Approximate Bayesian methods to combine RT and EEG data in a joint-likelihood. This approach respects the relative reliability of each information source, and can furnish reliable individual parameter estimates in the face of sometimes unreliable individual data. To examine the performance of the approach, we compare its performance in recovering known (ground-truth) parameter values to another approach based on individual-specific maximum-likelihood estimation.
We chose a neurally-informed model of decision-making during a cued 2-alternative motion-discrimination task as an example model to demonstrate the approach. The decision process was modelled as a race between two thresholded motor signals: RTs were modelled as the time taken for the first racing motor-signal to hit a threshold, plus motor-execution time, while beta-activity was modelled as the trajectory of the motor-signal plus EEG noise. Ten sets of model parameter values were generated by adding independent noise to each previously obtained best-fitting parameter, and these parameter sets were used to simulate single-trial RT and Beta-activity data for ten individuals. Parameter Likelihood was determined by applying Multivariate Kernel Density Estimation to simulated single-trial data, and an adaptive-MCMC algorithm (Haario, 2001) was used to sample from the Posterior distribution. For comparison, we also used a Particle-Swarm search to determine the Maximum-Likelihood (ML) parameter estimates for each individual separately.
The 95% Highest Posterior Density regions contained the ground-truth values for all parameters. It is particularly noteworthy that parameter recovery was successful even in the case of a parameter set with an EEG signal strength set to 0. Posterior expected parameter values obtained through our hierarchical modelling approach were significantly better than ML estimates obtained for each individual separately. We plan to use this highly versatile procedure to investigate decision-making differences between real individuals.

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Poster

PSTR298. Computational Models for Decision-Making

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Topic: H.03. Decision Making

Support: NIH Grant T32NS115704
NIH NIDA K01 DA033347

Title: Investigating a Neurocomputational Basis of Effort-Based Decision Making in Substance Use

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Abstract: Effort-based decision making evaluates the magnitude and probability of receiving a reward in relation to the effort required to obtain it. If effort expenditure is perceived as increasingly costly, the choice becomes devalued. Dopamine modulates effort-based decision making, as shown in human and animal studies, indicating that increasing or decreasing dopamine transmission enhances or diminishes (respectively) the willingness to expend effort for rewards. Dopamine has also been shown to be affected by chronic substance use, such that over time production, transmission, absorption, and sensitivity to dopamine is altered. However, it remains unclear whether effort-based decision making is affected by the chronic use of substances that affect dopamine. To address this knowledge gap, we investigated the neurocomputational basis of effort-based decision making and its alteration among groups characterized by tobacco use history. Compared to traditional analytic approaches, computational models account for complex relationships and patterns, trial-by-trial changes, feature extraction, and exploratory analysis. In this study, cigarette Smokers (n = 24), Ex-smokers (n = 17), and Never-smokers (n = 23) completed an effort-based decision making task that manipulated reward magnitude and probability for high and low effort options. Computational models were used to assess the subjective value of the high and low effort options based on reward magnitude, reward probability, and effort expenditure, which influences the decision between the high and low effort options. Group differences were revealed in the use of reward magnitude, reward probability, and effort expenditure to modify the subjective value of the choices. Never-smokers modified their subjective value more using effort expenditure (p-value<0.001), whereas Ex-smokers and Smokers modified their subjective value more using reward probability (p-value<0.001). Further, reward probability and reward magnitude were found to have a significant interaction for Never-smokers (p-value<0.001) and Ex-smokers (p-value = 0.004), indicating that the effect of reward probability on subjective value depends on the reward magnitude, whereas this interaction was not present for Smokers. Together, these results suggest that chronic tobacco use affects effort-based decision making. Understanding a neurocomputational basis of effort-based decision making in chronic substance use may enhance our comprehension of both typical and atypical effort-based decision making. These contributions hold the potential for translational utility in the diagnosis and treatment of substance use.

Disclosures: K.P. Spry: None. **K.T. Kishida:** None. **M.A. Addicott:** None.

Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.14/TT14

Topic: H.03. Decision Making

Support: NSFC 32271149

Title: Elucidating the circuit mechanism underlying task-dependent representational geometry of perceptual decisions

Authors: *Y. ZHANG[1], X. SHEN[2], G. OKAZAWA[3], B. MIN[4];
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Abstract: Understanding how neural population dynamics represent perceptual decisions is a central question in cognitive neuroscience. Previous studies have shown that the average firing rate of neurons in the lateral intraparietal (LIP) area increases with supporting evidence during motion discrimination tasks. However, recent findings from a novel face discrimination task have challenged this classical view, revealing that LIP firing rates actually decrease with supporting evidence (Okazawa et al., 2021 Cell). These contrasting results arise because LIP population encodes decision formation on a curved manifold in state space. The observations call for a revision of circuit models for perceptual decisions. In this study, we present a revised circuit model using an innovative recurrent neural network training technique. First, we recapitulate a Wong-Wang-like circuit model (Wong & Wang, 2006 J Neurosci), which successfully explains the representational geometry of perceptual decisions in motion discrimination tasks, including the curved manifold phenomenon. Building upon this foundation, we develop a new model inspired by the observed single neural dynamics in the data, specifically addressing the initial dip during stimulus onset. Importantly, our modeling work demonstrates that the firing rate reversal phenomenon can be explained by the addition of a single neural population to the existing Wong-Wang-like model. This simple circuit mechanism offers insights into the task-dependent representational geometry of perceptual decisions. Our findings challenge and refine existing models, paving the way for future investigations into the intricate processes shaping cognitive phenomena.

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Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.15/TT16

Topic: H.03. Decision Making

Title: A dynamic log-odds computation drives time-based decisions

Authors: *M. GRABENHORST[1], N. HEIN[2], L. T. MALONEY[3], G. MICHALAREAS[4], D. POEPPEL[1,3];
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Abstract: Many decisions under uncertainty are shaped by environmental temporal dynamics. The underlying computations are commonly investigated in the context of evidence accumulation over time. However, decisions are often based on estimates of time itself and do not require accumulation of sensory evidence. Under such conditions, the computational primitives of time estimation in decision making are not well understood. Here we conceptualize decision making as a dynamic process based on estimation of elapsed time and probability, leading to choice between options. Building on our previous work on temporal anticipation, we test three hypotheses: 1) Humans infer the 'best-choice' probability over time based on the outcome of their decisions and adapt their choice behavior accordingly. 2) In such dynamic decision making, the uncertainty in time estimation is affected by 'best-choice' probability over time (e.g. large probability, small uncertainty). 3) The uncertainty in elapsed time estimation is affected by time itself, i.e. the scalar property (e.g. large time span, large uncertainty). We used a visual 'set' - 'go' task in which the 'go' cue probability was uniform across time and thus did not provide decision information. Participants were asked to respond as fast as possible to the 'go' cue by pressing one of two buttons which was followed by a feedback signal (correct/incorrect choice). Over trials, the feedback signal encoded the dynamic 'best-choice' probability, i.e. the probability which of the two options is likely correct as a function of time. Analysis of behavior indicates that participants used the feedback signal to infer the dynamic 'best-choice' probabilities. We report three main results: 1) A model based on the log-odds of the 'best-choice' probabilities (ln(P/1-P)) captured choices over time. 2) 'Best-choice' probability is negatively related to the uncertainty in elapsed time estimation, resulting in precise temporal estimates when probability is large. 3) The canonical model of elapsed time estimation (scalar property) only accounts for a minor part of the behavioral variance, highlighting the strong effect of probability on time estimation. In sum, our results demonstrate that a simple computation based on the log-odds drives decision dynamics in the absence of evidence accumulation.

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Poster

PSTR298. Computational Models for Decision-Making

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Topic: H.03. Decision Making

Support: Wellcome Trust (219572/Z/19/Z)
Tripartite Grant from SFI, under 19/US/3599

Title: Neural markers of normative belief updates in volatile environments

Authors: *E. PARÉS-PUJOLRÀS[1], S. P. KELLY[1], P. R. MURPHY[2];
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Abstract: In order to make accurate decisions in noisy or otherwise uncertain environments, agents need to integrate relevant information over time. In static environments, the optimal strategy for decision-making involves perfect integration of all available evidence. However, many real-life environments can change unpredictably. Recent normative modelling has shown that in such contexts, optimal decision-making requires agents to weigh evidence differently over time, and to pay special attention to signals indicating that a change may have occurred. In this study, we investigate how two prominent decision-related EEG signals, the centroparietal positivity (CPP) and motor beta lateralisation, may reflect such normative belief updating in volatile contexts.

Human participants (N = 20) monitored a set of checkerboard patches ('samples') appearing anywhere along a semi-circular arc in the lower visual hemifield. Sample locations were drawn from one of two overlapping Gaussian distributions. Participants viewed a maximum of 10 samples per trial, and the distribution from which sample locations were drawn could change during the trial with a fixed probability (hazard rate) of 0.1. Their task was to report what they inferred to be the 'active' distribution at the end of each trial.

Participants weighted later evidence more heavily in their choices, and upweighted surprising evidence. We fit several evidence accumulation models to participants' choices, and replicated previous findings showing that behaviour in this task is best captured by the normative model. In the neural domain, we found that both centroparietal signals and motor preparation responses evoked by each sample scaled with how much evidence it provided (i.e. its log-likelihood ratio, *LLR*), and were also modulated by how surprising the sample was, as expected from normative computations. Motor signals, but not centroparietal ones, additionally reflected prior beliefs.

Our results suggest that centroparietal signals encode the effective magnitude of sample-by-sample belief updates (i.e. *LLR* modulated by decision-relevant contextual variables, like surprise in our context) rather than tracking the decision variable across samples. By contrast, motor beta lateralisation reflects the current state of the decision variable, encoding both prior belief at the time a sample is presented and the belief update evoked by the new information. Our results provide new insight into the long-standing question about which aspects of a decision drive signals like the CPP and beta lateralisation, and pave the way for future work assessing the interplay between them.

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Poster

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Topic: H.03. Decision Making

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Title: Dynamic cognitive control states exhibit widespread distributed encoding in multiple brain regions

Authors: *D. B. DORMAN[1], A. L. SAMPSON[2], P. SACRÉ[3], J. A. GONZÁLEZ-MARTÍNEZ[4], V. STUPHORN[2], E. NIEBUR[2], S. V. SARMA[1];
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Abstract: Cognitive control is critical for making goal-directed decisions and inhibiting biased behavior, and its deficits are associated with many neuropsychiatric disorders. Thus, predicting internal cognitive control states from neural data would have broad therapeutic impact. However, quantifying internal cognitive states from behavior to identify neural correlates remains challenging—for instance, cognitive control may fluctuate over time, requiring a method to identify dynamic cognitive control from behavior. Here, we use a state space modeling approach to model dynamic internal cognitive control during a gambling task and identify its neural correlates from intracranial EEG data. Intracranial (stereotactic) EEG was recorded from patients undergoing surgical monitoring for epilepsy while performing a simple card game in which participants drew from a uniform deck and then bet either $5 or $20 that their card would be higher than the computer card. A dynamical model with time-varying weights was fit to participant bets to estimate cognitive control. The model used a logistic choice function to predict bets based on both rational choice variables (expected return and expected risk given current card value) and history-dependent bias variables (recent reward prediction error and card history), and the weights of the bias variables varied over time. The cognitive control signal was then quantified as the ratio of the rational choice weights to bias weights. This allowed us to decouple bias from cognitive control, as participants may experience a high bias but still inhibit that bias on a given trial if their control state is high. Neural correlates of the cognitive control signal were computed by first computing wavelet spectrograms and then computing correlations using a nonparametric cluster statistic on the spectrotemporal data to find regions in time-frequency space for each brain region that were correlated with cognitive control signals. We found that dynamic cognitive control states accurately predicted choices and found that these states exhibited significant correlations with neural time-frequency data across multiple brain regions, including occipital, parietal, and frontal areas. Our results indicate widespread distributed encoding of cognitive control, suggesting that higher level visual areas may experience top-down modulation by cognitive control to attend to critical visual information informing decision making. Together, by decoding cognitive control from behavior and identifying its neural correlates, this work has implications for improving neuromodulatory therapeutic treatments for disorders of cognitive control.

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Poster

PSTR298. Computational Models for Decision-Making

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Science Foundation Ireland Grant 21/PATH-S/9643
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The Wellcome Trust Grant 219572/Z/19/Z

Title: Biases in motion direction estimation are consistent across response effectors

Authors: *E. A. CORBETT[1,2,3], S. M. MORAN[2], P. L. SMITH[4], S. P. KELLY[1,2], R. G. O'CONNELL[2,3];
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Abstract: When people perform perceptual decisions with outcomes on a continuum, they frequently exhibit consistent, but idiosyncratic, biases in response choices and response times. However, it is unclear whether the observed biases might actually be tied to motor responses, as opposed to the perceptual decision process (Topfer et al 2022). To test this, we conducted a study in which six participants reported the perceived direction of motion (spanning 360º) from a random dot kinematogram stimulus at two interleaved coherence levels, in alternating blocks using joystick and eye movement response modes. Responses were made on a circle that surrounded the stimulus. Response times were taken as soon as the response movement was initiated, at which time the stimulus disappeared. Participants were provided feedback on the response movement they made. In the joystick task, a cursor appeared on the screen once the movement was initiated and participants were encouraged to make a ballistic movement to the chosen position on the response circle. With the eye movement, the registered gaze position was displayed to the participant once the response movement was complete. Each participant completed more than 2400 trials in total over four sessions.
We jointly fit individuals' response angles and response times with the circular diffusion model, accounting for encoding failures in the low coherence trials through a mixture component with uniformly distributed drift rates. We fit the directional variation through stimulus biases using the similarity-choice method of Smith et al (2020, 2022), in which the drift rate is the vector sum of the encoded metric (true stimulus direction) and categorical (participant-favoured directions) representations of the stimulus. We jointly fit the data from all conditions, allowing the decision criterion and non-decision time parameters to vary across response modes. We found that the

biases were highly consistent; models with categorical bias parameters shared across the eye and joystick movement data performed better for all participants than those in which the bias parameters were free to vary across response modes, with an average difference in Akaike Information Criterion (AIC) of 12. This result suggests that in this task context in which participants were provided with feedback of their response movement, the behavioural biases largely reflect perceptual decision processing rather than the movements themselves.
References:
Smith, Corbett & Lilburn (2022). Psychol. Rev.
Smith, Saber, Corbett & Lilburn (2020). Psychol. Rev. 127-4, 562-590.
Topfer et al (2022). J. Vision, 22-16.

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Poster

PSTR298. Computational Models for Decision-Making

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR298.19/TT20

Topic: H.03. Decision Making

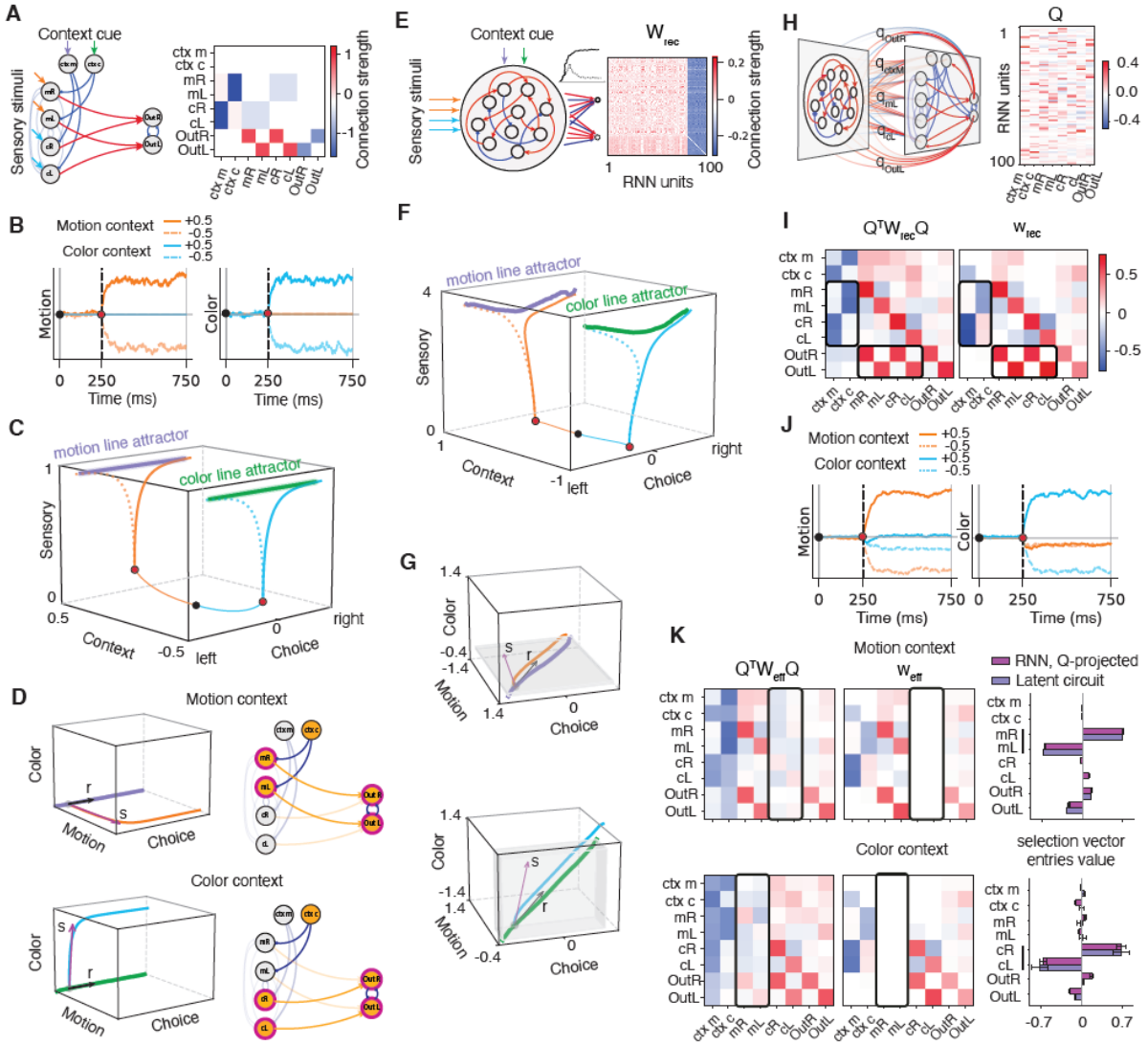
Support: RF1DA055666

Title: A neural circuit mechanism for context-dependent selection via population dynamics

Authors: *P. TOLMACHEV[1], C. LANGDON[2], T. A. ENGEL[2];
[2]Princeton Neurosci. Inst., [1]Princeton Neurosci. Inst., Princeton, NJ

Abstract: The ability to flexibly select relevant stimuli for guiding behavior in different contexts depends on the prefrontal cortex, but the underlying mechanisms are unknown. Traditional hand-crafted neural circuit models hypothesize a suppression mechanism in which the persistent activity of neurons representing context inhibits responses to irrelevant stimuli. On the other hand, reverse-engineering recurrent neural networks (RNNs) trained on context-dependent tasks revealed an emergent mechanism for the flexible selection of relevant stimuli via population dynamics. In RNNs, within a given context, only the inputs aligned with a "selection vector" drive the activity along the line attractor, a continuum of fixed points aligned with the output dimension. In contrast to the inhibitory mechanism, this selection-vector mechanism does not seem to require the suppression of irrelevant stimuli. Yet, it is unclear what circuit structure gives rise to the selection vectors and whether the suppression and selection-vector mechanisms are fundamentally different.
We show that the selection of relevant stimuli via population dynamics can arise from the suppression of irrelevant stimuli. First, we construct a minimal neural circuit model based on the suppression mechanism and show that the circuit dynamics implement the selection-vector mechanism. In reverse, we establish a correspondence between the suppression and selection-

vector mechanisms in RNNs trained on a context-dependent task via backpropagation. We fit RNN responses with a latent circuit model to obtain a low-dimensional mechanistic model of task-related dynamics in the RNN.The latent circuit model revealed the suppression of irrelevant stimulus representations in the RNN, which led to fading of the effective connectivity leading to context-dependent changes in the selection vector.This work links the dynamical-systems description of cognitive computations to the underlying circuit structure, opening new possibilities for causal manipulations of the neural networks to validate these mechanisms in experiments.



Disclosures: **P. Tolmachev:** None. **C. Langdon:** None. **T.A. Engel:** None.

Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR298.20/TT21

Topic: H.03. Decision Making

Title: Mapping sequential sampling models onto the activity of populations of neurons via the Laplace transform

Authors: *R. KIRKPATRICK[1], M. W. HOWARD[2], P. B. SEDERBERG[3];
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Abstract: Over the last fifty years, mathematical psychology has developed a class of sequential sampling models to describe evidence accumulation in simple decisions. These models including the diffusion decision model, race models, leaky accumulator models, and leaky competing accumulator models, have been extensively studied behaviorally. Different behavioral experiments have found evidence favoring different models, which can all be understood as distinct parameterizations of a more general cognitive model (Bogacz et al., 2006). The mapping between these cognitive models and populations of neurons in the brain has been a subject of intense interest over recent years, with many authors proposing recurrent neural networks as evidence accumulation circuits. However, the mapping between recurrent neural networks and the different sequential sampling models is unclear. Here we present a theoretical framework that maps these sequential sampling models onto populations of neurons via the Laplace transform and the inverse Laplace transform circuits. These circuits are a special case of recurrent neural networks that have found strong support in the neuroscience of representations of time in memory. Different cognitive models are implemented precisely as different parameterizations of a canonical neural circuit. Neurons in the Laplace representations show monotonic ramping as a function of evidence; neurons in the inverse Laplace representations show circumscribed receptive fields. By studying the covariance matrices of the Laplace and inverse spaces, we find that populations obeying these equations can give rise to sensible low-dimensional dynamics as well as rotational dynamics under appropriate circumstances. Finally, formulating the evidence accumulator in Laplace space leads naturally to a neural representation of evidence as a function of time, which could be used to construct neurocognitive models of decision-making under time pressure and resource rational planning.

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Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.21/TT22

Topic: H.03. Decision Making

Support: Swartz Foundation
US National Institutes of Health (NIH) grant R01MH062349

Title: Neural circuit underlying economic decisions: insights from a computational model

Authors: *A. BATTISTA[1], C. PADOA-SCHIOPPA[2], X.-J. WANG[1];
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Neurosci., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Understanding the neural underpinnings of economic choices is fundamental in neuroscience. We present a computational model that sheds light on the neural circuitry instantiating the decision process. Our study utilizes excitatory-inhibitory recurrent neural networks trained with state-of-the-art reinforcement learning algorithms to simulate decision processes in which individuals assign values to available goods and make choices based on their subjective preferences. Analysis of trained networks reveals three types of neurons reminiscent of those observed in the primate orbitofrontal cortex (OFC). These neurons encode the value of individual goods, the value of the chosen good, and the choice outcome. Notably, their activity is independent of spatial contingencies, supporting a good-based model of economic decisions. Furthermore, the dynamics of the networks are low-dimensional, with the relevant dimensions - which explain most of the variance - associated with decision quantities. We extend the model to more complex choice paradigms, including tasks involving multiple features (e.g., quantity and probability), ternary, sequential, and bundled offers. Our network can generalize to new situations akin to real-world decision scenarios.This model challenges previous theoretical assumptions by revealing an heterogeneous activity among the three types of neurons. Unlike prior models, our network does not impose constraints on the functional role of excitatory and inhibitory cells. In particular, it allows for either excitatory or inhibitory neurons encoding the chosen value. This divergence aligns with observations of decision-related neurons in OFC and highlights the importance of considering more diverse neural responses in economic choice contexts.Importantly, we uncover a categorical representation of decision variables, contrasting with a category-free representation found in other prefrontal areas. A recurrent connectivity matrix analysis reveals a highly structured, low-rank pattern indicating low-dimensional population dynamics within the network. We further develop a reduced circuit model based on our trained networks, illustrating winner-take-all dynamics between pools of offer value cells as a mechanism for decision solving.Our study offers novel insights into the neural circuits and dynamics underlying economic decisions. The findings provide a foundation for future investigations, offering testable predictions that could be examined in future experimental studies.

Disclosures: A. Battista: None. **C. Padoa-Schioppa:** None. **X. Wang:** None.

Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.22/TT23

Topic: H.03. Decision Making

Support: R01NS110806

Title: Spectral dynamics in slow brain wave oscillons

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Abstract: Discrete Padé Transform (DPT) is a recently developed computational method that allowscarrying nuanced analyses of the brain waves' structure. In particular, it reveals a novel,detailed picture of the brain wave dynamics1. By applying DPT technique to analyzing thelocal field potential (LFP) recorded in the CA1 area of rat's hippocampus, we found a newlevel of structure—a set of discrete waves with time-modulated frequencies, which we calloscillons. The frequency domains occupied by the individual oscillons roughly correspond tothe frequency bands attributed to the traditional, Fourier-defined brain waves. In particular,the spectrum of the lowest-frequency oscillon occupies the θ-band (about 4-12 Hz) and thenext oscillon changes at the slow-γ; rate (20-45 Hz). By analyzing the LFP data recordedduring active movements, we found that the mean frequencies and the amplitudes of the θand slow-γ; oscillons are coupled to the animal's speed, which parallels the behavior of theFourier-defined θ and slow-γ; waves. We then studied the dynamics of the embeddedfrequencies in the oscillons' dynamic spectra—the spectral waves, using Welch spectraldecomposition. We demonstrate that embedded frequencies in both oscillons exhibit complexbehaviors at several timescales2. In particular, we observe slow frequency alterations thatmay be attributed to endogenous CA1 network dynamics, and some rapid changes that mayreflect abrupt external inputs from the CA3 area or from the medial entorhinal cortex. Theseresults qualitatively expand the scope of the hippocampal oscillons' properties and shed newlight on the structure and functionality of synchronized neuronal activity in hippocampocortical circuits.Reference: (1) Perotti L, DeVito J, Bessis D, Dabaghian Y. Discrete Structure of the Brain Rhythms. Sci Rep.2019;9(1):1105. doi: 10.1038/s41598-018-37196-0. (2) Zobaer MS, Domenico CM, Perotti L, Ji D, DabaghianY. Rapid Spectral Dynamics in Hippocampal Oscillons. Front Comput Neurosci. 2022;16:880742. Epub20220610. doi: 10.3389/fncom.2022.880742. PubMed PMID: 35757231; PMCID: PMC9226310

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Poster

PSTR298. Computational Models for Decision-Making

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR298.23/TT24

Topic: H.03. Decision Making

Support: NSF CAREER Award 204611
Carney Institute for Brain Science Innovation Award
Brown OVPR Seed Award
NIH T32 MH126388
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Title: Decomposing the neurocomputational mechanisms of reward and aversive motivation on mental effort allocation

Authors: *D. YEE, M. PRATER FAHEY, X. LENG, M. TARLOW, J. KIM, K. MUNDY, S. NEVINS, A. SHENHAV;
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Abstract: Humans demonstrate a remarkable ability to determine when and how much effort to allocate based on the expected positive or negative outcomes (e.g., bonus earned or job termination). Here, we aim to identify the neural and computational mechanisms underlying the dissociable influence of reward and punishment in shaping mental effort allocation. We combine computational modeling and fMRI to test a key prediction of the Expected Value of Control (EVC) theory, which organizes a neural circuit around temporally distinct sub-processes that underlie the 1) evaluation of positive vs. negative incentives, 2) integration of those incentives to decide how to allocate control, and 3) exertion of the chosen control. 100 college-student participants (58F, 18-23 years) performed a multi-incentive control task, where they could earn monetary bonuses for correct responses and were penalized with monetary losses for errors. We characterized task performance with a drift-diffusion model (DDM) and found that reward promotes attentional control via increasing the rate of evidence accumulation (drift rate v; p=.003), whereas punishment promotes caution via increasing response threshold (threshold a; p<.001). Our fMRI results revealed a network of regions that encoded higher potential rewards (e.g., striatum [Str]: p=.009; dorsal anterior cingulate cortex [dACC]: p=.002). A distinct network encoded higher potential penalties (e.g., anterior insula [AI]: p=.003; Lateral Prefrontal Cortex [LPFC]: p<.001; Inferior Frontal Gyrus [IFG]: p=.004). Model-based fMRI analyses revealed that components of these networks were associated with distinct forms of control allocation. Several of these regions were further associated with variability in control allocation on the upcoming trials, with IFG activity for instance predicting increases in threshold (p<0.001). Preliminary analyses of separate dACC networks delineated by membership in distinct functional networks (salience attention [dACC-sal] vs. frontoparietal control [dACC-ctrl]) revealed a dissociation whereby dACC-sal was more closely associated with changes in drift rate (p<.001) whereas dACC-ctrl was more closely associated with changes in threshold (p=.007). These regions further modulated the influence of specific incentives on control adjustments (e.g., dACC-sal interaction reward is associated with threshold (p<.001), and dACC-ctrl interaction with reward is associated with drift rate (p=.04)). These data provide novel evidence for the neurocomputational circuitry underlying the integration of positive and negative incentives into the Expected Value of Control.

Disclosures: D. Yee: None. **M. Prater Fahey:** None. **X. Leng:** None. **M. Tarlow:** None. **J. Kim:** None. **K. Mundy:** None. **S. Nevins:** None. **A. Shenhav:** None.

Poster

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Topic: H.03. Decision Making

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Title: Modeling of abstract reasoning using a graph neural network framework

Authors: *Q. DO[1], C. AHN[4], J. GUO[1], L. BAKST[2], J. T. MCGUIRE[1], C. E. STERN[3], M. E. HASSELMO[2];
[2]Psychological & Brain Sci., [3]Ctr. Memory & Brain, [1]Boston Univ., Boston, MA; [4]Grad. Program for Neurosci., Boston Univ. Grad. Program For Neurosci., Boston, MA

Abstract: Abstract reasoning is a hallmark of human intelligence and remains a challenging feat for state-of-the-art artificial intelligence systems. Designing a framework that captures fundamental aspects of abstract reasoning would not only push the limit of artificial systems, but also broaden our current understanding of human thinking and reasoning abilities. To this end, we have focused our efforts on modeling potential mechanisms using the Abstraction and Reasoning Corpus (ARC). In a trial within the ARC task, given a small set of puzzle-and-solution pairs, a solver must identify and apply a rule to a novel puzzle to construct a solution. The task provides a useful benchmark for testing human-like reasoning ability given limited observations, as initial work across multiple groups, including our own, has demonstrated that humans are adept solvers while AI systems fall short. We built a modeling framework where abstraction is the equivalent of constructing different graph representations given visuospatial inputs. Reasoning is modeled by transforming an input graph into an output graph via a multilayered perceptron (MLP) network. Attaining the right level of abstraction for the reasoning demands is the equivalent of choosing the graph representations such that the MLP can be trained using a few examples within a handful of iterations. We demonstrated the applicability of our framework to the ARC and showed that the trained MLP - driven by suitable graph representations - can exhibit few-shot learning and is capable of discovering specific rules. This framework also generates predictions for human problem-solving. In particular, the model suggests that problem-solving could be subdivided into distinct processes: identifying an appropriate level of abstraction and optimizing the input-to-output transformation.

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Poster

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Topic: H.03. Decision Making

Support: the Kavli Foundation
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BBRF NARSAD

Title: Choice biases during learning reflect strategic exploration

Authors: *Z. ZHU[1], K. KUCHIBHOTLA[2];
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Abstract: Humans, even as infants, use purposeful cognitive strategies such as exploration and hypothesis testing to learn about causal interactions in the environment. In animal learning studies, however, it has been challenging to disentangle potential purposeful strategies from errors arising from imperfect knowledge or inherent biases. Here, we trained head-fixed mice on a wheel-based auditory two-choice task and exploited the intra- and inter-animal variability to understand the drivers of errors during learning. Early in learning, rather than choosing randomly or based on immediate trial history, mice displayed a strong bias towards a given choice (left or right). This choice bias was dynamic - continuing for tens to hundreds of trials, before switching abruptly to an unbiased state or to the other side, ruling out inherent motor biases. Moreover, biased states coincided with rapid motor kinematics, reflecting less deliberation and more directed choice exploration. Finally, throughout learning we introduced 'catch' trials (correct choices that are not reinforced) followed by a block of ten non-reinforced trials. During these blocks, animals performed significantly better with less bias, abruptly changing strategies to exploit their acquired cue-response learning to test for potential changes in outcome contingencies. These findings argue that rodents actively probe their environment in a directed manner, potentially engaging in a rudimentary form of hypothesis testing to refine their decision-making and maintain long-term flexibility.

Disclosures: Z. Zhu: None. **K. Kuchibhotla:** None.

Poster

PSTR298. Computational Models for Decision-Making

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Topic: H.03. Decision Making

Support: National Science and Technology Innovation 2030-Major Projects-2021ZD0203700-1

Title: Confidence bias implies the underlying decision-making mechanism

Authors: *F. SUN[1], Y. NI[2], W. LU[1], J. SU[1], S. WANG[1], N. LIU[3], X. WAN[1];
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Abstract: When dissecting the decision-making process, we often pay close attention to the characteristics of choices and response time. However, several computational models could produce the similar statistics of choice and response time while reflecting different neuro-computational mechanisms. Therefore, only used choices and response time may not be sufficient to measure human decision-making behavior. Confidence report about the decision is correct is another important feature of decision-making that could provide additional insight into the neuro-computational mechanism of decision-making. To investigate this, we recruited male and female participants to perform a perceptual (n=28) or a value-based (n=27) decision-making task and report their confidence inside the magnetic resonance imaging (MRI) scanner. We found that the participants' confidence ratings were systematically biased towards the chosen option across both tasks, regardless of whether the choices were correct or not. By contrast, their choices were equally accounted for by the evidence of both options, and the objective accuracy also remained unbiased. We also found that confidence bias was not only present in behavior but also in neural activity. The dorsal anterior cingulate cortex (dACC) activities, which represented confidence commonly across both tasks, was also biased to the chosen option. Furthermore, the representation of the confidence related bias in the brain was not separate from the decision variable. To capture this confidence bias, we used variants of drift diffusion models to fit with the participants' behavioral data. The best-fitting model was the one equipped with both mutual inhibition and an urgency signal and only this model could replicate the confidence bias which is confirmed by simulation. We also found a relationship between bias strength and model parameters, especially the mutual inhibition strength. Further analysis on the decision-making dynamics pointed out that winner-take-all states caused by mutual inhibition were crucial for the confidence bias. These findings suggest that mutual inhibition and an urgency signal are indispensable components of neurocomputational models accounting for the decision-making process.

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Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.27/TT28

Topic: H.03. Decision Making

Support: DFG, Collaborative Research Center SFB TRR 169 “Cross-modal learning”.

Title: Communicating with surprise - a novel computational model for Tacit Communication Game

Authors: *T. BUIDZE[1], Y. YAO[2], J. P. GLAESCHER[3];
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Abstract: Traditionally, expectation violations signal the need for improvement of predictions through learning, but during communication, surprise can be used intentionally to direct the attention of the Receiver of a message toward relevant information. In language-based communication, this is accomplished by creating salient events within a message through verbal and prosodic cues (e.g., raising the voice). However, in unfamiliar settings without a shared language, the mechanism of effective communication remains poorly understood. Here we propose that the intentional use of unexpected events, or surprise, can effectively communicate goal-relevant information by defying expectations. We test this mechanism in the context of Tacit Communication Game (TCG), a non-verbal communication game played on a square grid board, where the Sender must convey the Receiver’s goal location through her movement patterns (‘messages’). By observing the message, the Receiver infers his goal location. We developed a novel computational model for the Sender’s message design that is based on the idea of communicating through surprise: it uses intuitive priors based on principles of movement kinetics and goal orientation and constructs messages step by step by maximizing information-theoretic surprise at the Receiver’s goal state. We compared our model against an existing Theory of Mind belief-updating model, which selects messages through exhaustive search and updates beliefs based on the Receiver's success, but lacks step-by-step predictions. We fit both models to the behavioral and eye-tracking data obtained from two data sets consisting of 29 and 31 pairs of participants playing the roles of Sender and Receiver in the TCG. The participant's behavioral data (message type, message profile, i.e., the number of moves in either direction) was better described by the surprise model than by the belief updating model. The Pupillary Dilation Response was also positively associated with the model-derived surprise signal across all participants, consistent with its role in detecting unexpected events. Our results indicate that in a novel environment, surprising events can be intentionally deployed to guide the Receiver’s attention and goal orientation, and therefore convey the communicative intention of the message more effectively.

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Poster

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Topic: H.03. Decision Making

Support: NIH Grant 1R01MH126971-01A1.

Title: A generalized computational model of learning structures in time

Authors: *N. RAZMI[1,2], M. R. NASSAR[2];
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Abstract: Intelligent behavior in biological systems requires storage and retrieval of knowledge in a dynamic world where sensory experiences are informed by context and memory. Yet theoretical, and computational accounts of learning in humans and animals normally consider learning in isolated contexts or stationery environments. We begin to address this problem with a normative approach of inferring latent contexts in a predictive inference task previously used to study adaptive learning. Outcomes in the task are generated from "contexts" that change in a structured but discontinuous manner, i.e., context can persist, change abruptly, or return to a previously seen one. This dynamic is formalized in the standard Markov process language with a "matrix of transition probabilities". To learn this task, we use a normative approach, specifically using a nonparametric Bayesian model, endowed with hyperparameters that control the probabilities of creating a new cluster or expressing a previously seen cluster in addition to a cluster persistence factor. Inverting this generative model with Bayes rule can facilitate exact or approximate inference on the hidden context for a given set of hyperparameters. Here we implement this Bayesian inference model and extend it to simultaneously do inference over hyperparameters, thereby allowing it to "learn" the structure of the environment. We then compare the qualitative behavior of this generalized model, specifically the trends in accuracy and learning rate changes throughout the course of learning the task, to previously observed results in human participants doing similar tasks. More specifically, human participants have been reported to be sensitive to big changes in the environment (i.e., big prediction errors) by increasing their learning rate when changes are thought to come from a persisting cause whereas insensitive to big changes when they are indicative of oddball trials. They are also able to learn to predict outcomes generated from a repetitive sequence of contexts (reversal learning or sequence learning tasks). We believe that most computational models have not yet considered the problem of learning the whole range of different temporal structures that exists in neural and behavioral experiment data from scratch and still lack predictions for what might be the neural substrates of learning structures in a temporally dynamic world.

Disclosures: **N. Razmi:** None. **M.R. Nassar:** None.

Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.29/UU2

Topic: H.03. Decision Making

Support: SFB1528

Title: Theory of Mind during cooperative and competitive interactions in a social foraging task

Authors: *S. KHONEIVEH[1], J. GLÄSCHER[2];
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Abstract: Theory of mind (ToM) involves cognitive abilities, to construct mental models of others to predict their behavior. Such mental models are commonly referred to as 1st level ToM ("I think you will choose X."). When the mental models include the other person's model of oneself, ToM becomes recursive, referred to as 2nd level ToM ("I think you think I will choose Y."). Some studies argue that ToM sophistication varies across interactional contexts: in competitive situations humans reason at a higher ToM level because they have to anticipated and compensate the strategic choices of their opponents. However, during cooperation involving action coordination a sophisticated mental model that predicts the partner's action based her mental model about me is also beneficial. Here, we investigate whether transitioning between these interactional contexts leads to changes in ToM levels or whether the ToM sophistication is maintained. To address this issue, we designed a novel Social Foraging Task (SFT), in which participants first have to make foraging decision by selecting between different patches with cooperative (Stag Hunt game), competitive (Hide and See game), or independent decision-making tasks in each trial. We administrated the SFT to 74 pairs of participants in an online experiment. Model-free analyses of the reaction times(RTs) after removing the commonly observed unspecific acceleration of RTs through exponential curve fitting, revealed significantly prolonged RTs during competitive play suggesting and increase mental effort possibly due to higher ToM sophistication. We then developed a computational ToM model that estimates beliefs about the co-player at each levels of the ToM hierarchy. Unlike existing ToM models, our approach also dynamically updated the choice strategy at the lowest level (L0) on which higher ToM levels are built. The preferred ToM level is estimated based on prediction accuracy at each level. We investigated whether different interactional contexts elicited changes ToM levels or whether they remained constant during context switches. Comparing these model variants using the Bayesian Information Criterion (BIC), we found support for a change in ToM levels in the SFT suggesting that humans can efficiently recruit sophisticated recursive reasoning strategies of different complexity if it is beneficial in the respective interactional contexts.

Disclosures: S. Khoneiveh: None. **J. Gläscher:** None.

Poster

PSTR298. Computational Models for Decision-Making

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Program #/Poster #: PSTR298.30/UU3

Topic: D.07. Visual Sensory-Motor Processing

Support: Natural Sciences and Engineering Research Council of Canada (NSERC)

Title: Computational modelling of the dorsal and the ventral streams

Authors: *T. B. REZA[1], S. LUO[2], R. JAIN[2], J. CAI[3], M. NIEMEIER[1];
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Abstract: The brain divides the processing of visual information into two separate neural streams: the ventral stream, responsible for perception, and the dorsal stream, responsible for action. The dorsal stream translates visual characteristics into motor commands (i.e., grasping), typically modelled as a regression task in artificial neural networks (ANNs). Grasp representation in ANN involves taking visual data of an object and configuring suitable grasp points on an object. In contrast, the ventral stream converts retinal images into abstract representations for object recognition, which is modelled as a classification task in ANNs. It has been hypothesized that differences between the two streams are due to differences in how the two streams are optimized. Consistent with this, neural networks trained for object classification or to steer robotic grasp movements yield different response properties. However, these networks differ in architecture and training. To gauge the influence of task-specific training differences, we designed a novel map-based ANN and a task-agnostic double-log loss function suitable for classification and visual grasp analysis. Our method penalizes boundary predictions for both tasks, allowing a direct comparison between classification and grasping networks with identical optimization rules. To understand the emerging difference between the two pathways we used representational similarity analysis revealed that our classification model, despite having similar optimization principles, exhibits activation patterns more like state-of-the-art classification models like AlexNet, while our grasp network shows greater similarity to models such as GR-ConvNet.Furthermore, Guided Backpropagation showed that the classification network emphasizes local information of object parts and surface features, while the grasp network focuses on global features. The emergence of dorsal and ventral stream-like properties suggests that our approach provides a fair and task-agnostic method to compare optimization trends across action-based and perception-based learning agents. Our approach contributes to a quantitative approach of modeling the visual cortex.

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Poster

PSTR299. Network Activity of Executive Functions

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Program #/Poster #: PSTR299.01/UU4

Topic: H.04. Executive Functions

Support: IARPA 2014-13121700004

Title: Joint Structure-Function Network Modeling of General Intelligence

Authors: *R. R. WILCOX[1], B. HEMMATIAN[1], E. D. ANDERSON[3], P. ROBLES-GRANDA[1], C. ZWILLING[1], A. NAYAK[2], L. R. VARSHNEY[2], A. K. BARBEY[1]; [1]Psychology, [2]Electrical and Computer Engin., Univ. of Illinois, Urbana, IL; [3]711th HPW, Air Force Res. Lab., Dayton, OH

Abstract: Network Neuroscience represents the brain as a complex information processing system made of discrete, interconnected regions that form locally- and globally-organized networks (Bassett & Sporns, 2017). The topology of the brain's structural and functional networks displays small-world properties, such that locally integrated sets of regions are connected via long-range projections (Bassett & Bullmore, 2017). Specialized 'connector-hub' nodes in small-world networks represent regions with high nodal degree and diverse connectivity across networks. They facilitate inter-network integration, considered a key biological mechanism underlying higher cognition (Barbey, 2021). To date, the relationship between connector hubs and cognition has been separately studied in the functional (Bertolero et al., 2018) and structural (Gu et al., 2015) domains. The findings motivate the use of joint-domain modeling to examine the role connector hubs play in cognition, as network topology reflects a balance between competing processing demands and structural constraints (Bassett & Sporns, 2017). We predict human intelligence using joint structure-function modeling of hub connectivity, derived from multimodal connectomes based on tractography and functional independent component analysis (Chu et al., 2018). By considering biological constraints on brain function, this approach produces assessments of connectivity that better reflect the underlying neurobiology of brain networks, while also accounting for common methodological issues in the estimation of structural pathways. We apply this method in a representative dataset of multimodal imaging and cognitive performance. Using a predictive cross-validation framework, our joint structure-function modeling approach predicts general intelligence ($R = 0.31$) more accurately than structure- ($R = 0.12$) or function-specific ($R = 0.03$) connectomes. Network participation coefficients further demonstrate that connector hubs mediate general intelligence. Incorporating the hubs' topological properties into models explains significantly more variance ($R^2 = 0.70$) than the joint structure-function model alone (Chu et al., 2018). Our results highlight the benefits of jointly modeling brain networks' structure and function to find the neurobiological properties that underlie individual differences in cognition.

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Poster

PSTR299. Network Activity of Executive Functions

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Topic: H.04. Executive Functions

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Title: Real-time regulation of arousal and performance in healthy non-human primates using the DyNeuMo-X bidirectional neuromodulation system

Authors: *J. BAKER[1], R. TOTH[2], A. DELI[3], M. ZAMORA[2], J. FLEMING[2], M. BENJABER[2], J.-W. RYOU[4], K. P. PURPURA[5], N. D. SCHIFF[6], T. DENISON[2];
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Abstract: The application of closed-loop approaches in systems neuroscience and the use of deep brain stimulation (DBS) and brain-computer interfaces (BCI) in neurology hold great promise for advancing our understanding of the brain and developing novel systems to restore lost function. Treatment-resistant brain disorders are increasingly viewed as dysfunctions in neuronal activity across widely distributed brain 'networks', and invasive neuromodulation strategies, like DBS and BCI, are emerging as promising therapeutic options. However, current systems have been optimized to treat Parkinson's Disease and Epilepsy, which significantly limits their application in emerging indications, where large-scale surface or depth recording and/or stimulation capabilities will be essential for an effective therapy. One emerging indication is the treatment of arousal dysregulation, which is hypothesized to contribute to cognitive dysfunctions in various neurological disorders, most prominently following a moderate to severe traumatic brain injury (msTBI) in humans. In a recently completed study (NCT02881151), we explored the use of daytime central thalamic deep brain stimulation (CT-DBS) to treat chronic dysregulation of arousal in five msTBI patients, and here CT-DBS was linked to improved executive attention and reduced mental fatigue. However, the mechanisms of this promising therapy are not well understood, and the development of novel bidirectional neuromodulation systems will need to be validated in large animal models before their exploratory use in humans. In this study, we explored the use of closed-loop CT-DBS to dynamically regulate the arousal 'state' of two healthy non-human primates (NHP) to restore behavioral performance. We used pupillometry, behavioral performance measures, and real-time analysis of ECoG signals to episodically initiate closed-loop CT-DBS by using a clinical-grade bidirectional neuromodulation research platform, the DyNeuMo-X, and we were able to restore behavioral performance in both animals. The internal DyNeuMo system is being used in three clinical trials in the UK across different conditions (NCT05437393, NCT05197816, NCT03837314), and the approach developed here demonstrates the safety and feasibly of rapidly testing adaptive CT-DBS protocols in large animal models. These proof-of-concept results support our long-term goal of developing bidirectional neuromodulation systems to monitor and influence the dynamics of arousal regulation, ultimately to treat cognitive dysfunctions in patients with structural brain injuries and other etiologies.

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options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds. **M. Zamora:** None. **J. Fleming:** None. **M. Benjaber:** None. **J. Ryou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds. **K.P. Purpura:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds. **N.D. Schiff:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds. **T. Denison:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds.

Poster

PSTR299. Network Activity of Executive Functions

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Topic: H.04. Executive Functions

Support: NIH 5R01NS100849-05

Title: Altered mid-frontal theta dynamics indicate failure to engage cognitive control for working memory in Parkinson's disease

Authors: *B. E. YEAGER[1], A. SINGH[2], A. I. ESPINOZA[1], R. C. COLE[1], N. S. NARAYANAN[1];
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Abstract: Patients with Parkinson's disease (PD) commonly have impairments of cognitive control. The neurophysiological origins of these impairments in PD are unclear. It has been proposed that mid-frontal theta activity (~4-7 Hz) signals the need for cognitive control mechanisms needed to successfully resolve task demands in a goal-directed manner. Our prior work has shown that patients with PD have impaired cue-evoked mid-frontal theta activity. Here, we probed whether alterations in mid-frontal theta power extend to working memory tasks, as cognitive control is needed to simultaneously ignore task-irrelevant information and maintain information within working memory. We hypothesized that patients with PD have attenuated cue-evoked mid-frontal theta power compared to healthy adults in a working memory task. Scalp electroencephalography (EEG) was collected from 23 participants (9 PD, 14 healthy adults) while they completed a modified Sternberg memory test. Time-frequency analysis revealed lower mid-frontal theta power at the beginning of the encoding period for patients with PD

compared to healthy adults. These results suggest a similar neurophysiological signature between cue-triggered responding (Simon task) and working memory (Sternberg memory test) potentially representing the recruitment of cognitive control. In addition to mid-frontal theta power, we investigated changes in midline theta phase synchrony during the Simon and Sternberg tasks to further define electrophysiological alterations in PD. We hypothesized that patients with PD have reduced theta phase synchrony between mid-frontal and mid-parietal sources during both tasks compared to healthy adults. For the Simon task, data were analyzed from a previously collected dataset of 102 participants (64 PD, 38 healthy adults). Focusing again on cue-evoked theta activity, the weighted phase lag index (wPLI) was calculated between Cz and Pz sources which likely overlie major nodes of the salience and default mode networks involved in cognitive control. Strikingly, we found reduced midline theta phase synchrony in patients with PD compared to healthy adults during the Simon and the Sternberg tasks. These results indicate that both mid-frontal theta power and network connectivity are altered in PD. Overall, altered mid-frontal theta dynamics in patients with PD may indicate failure or difficulty to engage cognitive control, which may be a biomarker of disease-related cognitive changes.

Disclosures: B.E. Yeager: None. **A. Singh:** None. **A.I. Espinoza:** None. **R.C. Cole:** None. **N.S. Narayanan:** None.

Poster

PSTR299. Network Activity of Executive Functions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR299.04/UU7

Topic: H.04. Executive Functions

Title: Effects of carotid revascularization on cognitive function and brain functional connectivity in carotid stenosis patients with cognitive impairment

Authors: *M. KOHTA[1], Y. OSHIRO[2], Y. YAMAGUCHI[1], Y. IKEUCHI[1], A. FUJITA[1], K. HOSODA[1], K. TANAKA[1], S. MIZOBUCHI[2], E. KOHMURA[1], T. SASAYAMA[1]; [1]Neurosurg., [2]Anesthesiol., Kobe Univ. Grad. Sch. of Med., Kobe, Japan

Abstract: Background: Carotid stenosis can lead to both cognitive impairment (CI) and ischemic stroke. Although carotid revascularization surgery, such as carotid endarterectomy (CEA) and carotid artery stenting (CAS), can prevent future strokes, its impact on cognitive function is controversial. In this study, the authors examined resting-state functional connectivity (FC) in carotid stenosis patients with CI undergoing revascularization surgery, with a particular focus on the default mode network (DMN).Methods: Twenty-seven patients with carotid stenosis who were scheduled to undergo CEA or CAS between April 2016 and December 2020 were prospectively enrolled. A cognitive assessment, including the Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB), and Japanese version of the Montreal Cognitive Assessment (MoCA), as well as resting-state functional MRI, was performed 1 week preoperatively and 3 months postoperatively. In the analysis of FC, a seed-based analysis was

performed, where the seed was placed in the region associated with the DMN. The patients were divided into two groups according to the preoperative MoCA score: a normal cognition (NC) group (MoCA score ≥ 26) and a CI group (MoCA score < 26). The difference in cognitive function and FC between the NC and CI groups was investigated first, and then the change in cognitive function and FC after carotid revascularization was investigated in the CI group.Results: There were 11 and 16 patients in the NC and CI groups, respectively. The FC of the medial prefrontal cortex with the precuneus and that of the left lateral parietal cortex (LLP) with the right cerebellum were significantly lower in the CI group than in the NC group. In the CI group, significant improvements were found in MMSE (25.3 vs 26.8, p = 0.02), FAB (14.4 vs 15.6, p = 0.01), and MoCA scores (20.1 vs 23.9, p = 0.0001) after revascularization surgery. Significantly increased FC of the LLP with the right intracalcarine cortex, right lingual gyrus, and precuneus was observed after carotid revascularization. In addition, there was a significant positive correlation between the increased FC of the LLP with the precuneus and improvement in the MoCA score after carotid revascularization.Conclusions: These findings indicate that carotid revascularization, including CEA and CAS, might have positive impact on cognitive function by influencing brain FC in the DMN in carotid stenosis patients with CI.

Disclosures: **M. Kohta:** None. **Y. Oshiro:** None. **Y. Yamaguchi:** None. **Y. Ikeuchi:** None. **A. Fujita:** None. **K. Hosoda:** None. **K. Tanaka:** None. **S. Mizobuchi:** None. **E. Kohmura:** None. **T. Sasayama:** None.

Poster

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Program #/Poster #: PSTR299.05/UU8

Topic: H.04. Executive Functions

Title: Frontoparietal network stability predicts attentional control and cognitive flexibility

Authors: *S. LYONS, Z. IRVIN, B. DEPUE;
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Abstract: The frontoparietal network (FPN), comprised of the lateral prefrontal cortex (LPFC) and posterior parietal cortex (PPC), is highly involved in the recruitment of lower-level brain regions in the service of cognitive and behavioral task execution. Using dynamic resting state functional connectivity (rsFC) to understand how the FPN functions has emerged as a promising avenue to research the neural substrates of cognition and may be more sensitive at identifying its underpinnings. We investigated the intranetwork stability of the FPN and their contributions to cognition. We hypothesized that, generally, less stability of the FPN at rest would predict performance on both attention and cognitive flexibility. A total of 116 participants (62.9% female; Age = 33.8) from the NIMH Healthy Volunteer dataset were included. Participants completed a rsfMRI session and behavioral testing using the NIH Toolbox. Resting data were segmented into 20 windows of 60 seconds each with a 30 second overlap between windows.

Standard deviations between each ROI pair (6 pairs) were calculated for each window and were entered into two multiple linear regressions. The pooled variability of the overall model significantly predicted performance in the flanker task, $F(109, 116) = 2.7$, $p = .018$, $R^2 = .13$. Two specific ROI pairings indicated increased variability negatively predicted flanker performance [(right LPFC and left PPC); $\beta = -2.11$, $p = .004$], and positively predicted performance [(bilateral PPC); $\beta = 1.13$, $p = .048$]. Pooled variability of the overall model further predicted performance on the dimensional change card sort test, $F(109, 116) = 2.47$, $p = .028$, $R^2 = .12$. Again, the two specific ROI pairings significant in the flanker task indicated the same directionality of increased variability and performance in the dimensional change card sort test [(right LPFC and left PPC); $\beta = -2.21$, $p = .031$], [(bilateral PPC); $\beta = 1.86$, $p = .049$]. Our results add to existing literature connecting dynamic rsFC with both attention and cognitive flexibility. Variability of resting functional coupling within the FPN predicts the ability to deploy attention, as well as updating fluid task rules. Interestingly, paired variance among specific regions appears to influence cognitive functioning more than others, particularly between the right LPFC and left PPC and within the PPC, bilaterally. Functional instability between the right LPFC and left PPC potentially interferes with global attention to task relevant goals. However, increased variability was not always detrimental as greater functional instability between the bilateral PPC may subserve local attention to relevant task contexts.

Disclosures: **S. Lyons:** None. **Z. Irvin:** None. **B. Depue:** None.

Poster

PSTR299. Network Activity of Executive Functions

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Topic: H.04. Executive Functions

Support: NIMH Grant R01MH122613
1S10OD025025-01

Title: How Task Representations Integrate Information from Multiple Sources

Authors: *S. C. LEACH, H. MORROW, J. JIANG, K. HWANG;
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Abstract: The human brain is composed of distributed subunits that encode diverse sources of information. As such, the ability to integrate multiple streams of information to guide behavior is integral to cognitive flexibility. It is long thought that the frontoparietal system in the human brain is involved in integrative functions, however, how cognitive representations encoded in these regions support integration is not well understood. We propose a framework where integration is achieved by creating a joint distribution that encodes multiple task-relevant features to guide goal-directed behavior. In this framework, the degree of integration can be quantified by the statistical properties of this joint distribution. To test this framework, we

collected functional MRI data from 26 participants that performed a paradigm requiring them to integrate perceptual (color) information with non-observable state information to select the right task for the current trial. Each trial started with an array of red and yellow dots, in which the dominant color informs the task (face or scene judgement) subjects should perform, and the mapping between color and task randomly switched between two non-observable cognitive states. We used a Bayesian generative model to investigate integrative processes for this task. This model estimates, on a trial-by-trial basis, the subject's probabilistic belief on the cognitive state and perception of color. Critically, the model integrates these two probabilistic distributions of information into a joint distribution to encode the correct task they should perform. Using model-based fMRI analysis, we identified regions that encode the entropy of the joint distribution, as well as regions that encode cognitive state, color, and task representations. We also tested other key model-derived metrics, including the prediction error (PE) of state and task. When uncertainty in state and/or color was higher (i.e., greater entropy), dorsomedial prefrontal cortex (dmPFC), rostro-lateral PFC, and intraparietal cortex showed a greater BOLD magnitude. Moreover, decoding analyses successfully decoded task representation from these regions. Finally, in line with previous work, we found a greater BOLD magnitude in dmPFC and parietal cortex in response to a greater state PE. Our results support a framework where the integration of observable and non-observable information is achieved by creating a joint distribution that encodes multiple task-relevant features.

Disclosures: **S.C. Leach:** None. **H. Morrow:** None. **J. Jiang:** None. **K. Hwang:** None.

Poster

PSTR299. Network Activity of Executive Functions

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Program #/Poster #: PSTR299.07/UU10

Topic: H.04. Executive Functions

Support: Allen Institute

Title: Distributed context representations in the mouse brain during sensory task-switching

Authors: C. BENNETT, S. D. GALE, E. G. MCBRIDE, J. KUYAT, B. HARDCASTLE, H. CABASCO, A. SRIDHAR, C. MOCHIZUKI, R. GILLIS, H. BELSKI, H. LOEFFLER, S. DURAND, ***S. OLSEN**;
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Abstract: Humans and animals can flexibly control their behavioral responses to sensory stimuli based on goals and context. The mechanisms of signal routing in the brain supporting flexible sensory-action mapping are not well understood. We developed a task switching paradigm in mice that requires selective responding to either visual or auditory stimuli in blocks of trials. After block switches, mice rapidly shift the modality to which they respond. Standard reinforcement learning (*Q*-learning) does not capture fast switching dynamics, but adding a

context belief state to the RL model leads to better correspondence with mouse behavior. To characterize cortical and subcortical activity during task switching, we made multi-regional Neuropixels recordings. Within and across brain areas we observe diverse activity dynamics and coding by single neurons. At the population level, task context (visual-rewarded versus auditory-rewarded blocks) can be decoded from many brain regions including cortex, striatum, and midbrain. Moreover, behavioral errors are predicted by the trial-wise fidelity of this context representation. Average stimulus-evoked activity in early sensory areas does not differ between contexts, suggesting stimulus routing in this task is not mediated by simple gain modulation in these regions.

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Poster

PSTR299. Network Activity of Executive Functions

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Program #/Poster #: PSTR299.08/UU11

Topic: H.04. Executive Functions

Title: Propofol induced burst suppression evokes neuronal firing and local field potential traveling waves in the human brain

Authors: *V. ZARR[1], M. ALLEE[1], T. DAVIS[1], B. GREGOR[2], P. A. HOUSE[3], E. SMITH[1]; [1]Dept. of Neurosurg., Univ. of Utah, Salt Lake City, UT; [2]Sch. of Biol. and Hlth. Systems Engin., Arizona State Univ., Pheonix, AZ; [3]Intermountain Neurosci. Inst., Salt Lake City, UT

Abstract: 230 million people each year undergo general anesthesia. Despite substantial work, the spatiotemporal neural dynamics underlying medically induced loss of consciousness (mLOC) remain a mystery. Neural traveling waves are electrical perturbations that propagate across the brain with systematic phase delays. Recent work has characterized traveling wave propagation mechanisms in non-human primates (NHP) during mLOC and showed that they change directions. Prior work has shown the presence of burst suppression firing during mLOC. However, ours is the first study to characterize the spatiotemporal dynamics of traveling waves in human action potential and local field potential (LFP) activity during mLOC. We hypothesized that burst suppression evokes brain oscillations that propagate as traveling waves. We examined direct brain recordings during propofol induced loss of consciousness, from Utah-style microelectrode arrays from two adult patients with intractable epilepsy who were undergoing monitoring for surgical treatment for medically resistant seizures. Upon identification of burst suppression, we then regressed the timing of LFP and neuronal firing against the two spatial dimensions of the microelectrode array. We operationally defined traveling waves as regression models with slopes that significantly differed from zero, assessed via an F-test against a permutation distribution of N spatially shuffled LFP or firing times. We fit

these models with both L1 and L2 regularization for both signals, and controlled for false positives with permutation testing. We recorded a total of 96 LFPs and 71 single unit recordings for patient one. Out of 93 total bursts in patient one, traveling waves were identified from 30% of LFPs and from 54% of single unit recordings, using the L1 regularization regression model, respectively. Using the L2 regularization regression model, traveling waves were identified from 52% of LFPs and from 29% of single unit recordings, respectively. We recorded a total of 71 local LFPs and 96 single unit recordings for patient two. Of the channels recorded, traveling waves were identified from 14% of LFPs and from 27% of single unit recordings, using the L1 regularization regression model, respectively. Using the L2 regularization regression model, traveling waves were identified from 25% of LFPs and from 33% of single unit recordings. We therefore showed that neural activity during burst suppression propagated as traveling waves, suggesting that subsequent research into anesthesia burst suppression evoked traveling waves may identify spatiotemporal signatures of traveling waves that can differentiate among consciousness states.

Disclosures: V. Zarr: None. **M. Allee:** None. **T. Davis:** None. **B. Gregor:** None. **P.A. House:** None. **E. Smith:** None.

Poster

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NSF BCS #1932619

Title: A general theory of self interaction

Authors: *L. BRESTON[1], E. J. LEONARDIS[2], A. A. CHIBA[3];
[1]Univ. of California San Diego, LA JOLLA, CA; [2]Cognitive Sci., Salk Inst. for Biol. Studies, San Diego, CA; [3]Cognitive Sci., UC San Diego, San Diego, CA

Abstract: A central goal of neuroscience is to develop a parsimonious understanding of how cognition, perception, and action arise from the interactions between the brain, body, and environment. This goal is complicated by the system's tangle of interdependencies across many functional and structural scales which frustrates the traditional reductionist approach. Here we apply methods from statistical physics and dynamical systems to create a unified theory of internal and external processes. We treat the joint system as a macroscopic state with a given order parameter then model the dynamics of that abstracted value. We then use neural recordings from multiple brain regions in rats during self grooming as an experimental lens into these complex, self referential neuro-behavioral feedback loops. We then show how such loops can be

integrated into a control paradigm to actively maintain a state of criticality. By providing a unified framework for understanding how complex cognitive constructions can emerge from the same low-level neural processes that support behavior, this research has the potential to inform a range of science from future machine learning algorithm development to clinical treatments for issues involving mental health and mental distortions.

Disclosures: L. Breston: None. **E.J. Leonardis:** None. **A.A. Chiba:** None.

Poster

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Topic: H.04. Executive Functions

Support: R01AG063857

Title: Altered Brain Connectivity during Resting State as Electrophysiological Signatures in Cognitively Healthy Individuals with Pathological CSF Amyloid/tau

Authors: *A. MOHAMMED[1], C. MOLLOY[1], D. BUENNAGEL[1], A. N. FONTEH[1], R. BUTLER[1], M. KLEINMAN[4], R. J. ARECHAVALA[4], R. A. KLONER[2,3], X. ARAKAKI[1]; [1]Neurosci., [2]Neurosci. and 2Cardiovascular Res., [3]Cardiovasc. Res., Huntington Med. Res. Inst., Pasadena, CA; [4]Dept. of Envrn. and Occup. Hlth., Univ. of California, Irvine, Irvine, CA

Abstract: Alzheimer's disease (AD) pathology, including amyloid beta, the hyperphosphorylation of tau proteins, and inter-neuronal transmission, appears several years before AD symptoms. However, the effect of amyloid and tau (AT) pathology on resting-state (RS) electroencephalogram (EEG) connectivity in cognitively healthy (CH) Individuals remains unclear. A dataset of RS 21-channel EEG recordings with eyes closed was used from a total of 46 CH individuals according to their cerebrospinal fluid (CSF) amyloid/total-tau status, pathological (CH-PAT, n = 27) versus normal (CH-NAT or controls, n = 19). Brain volumetrics (e.g., MRI) and Heart rate variability (HRV) were assessed with NeuroQuant, and electrocardiogram (ECG), respectively. We analyzed and compared between CH-NATs and CH-PATs: 1) Effective connectivity (EC) between different brain regions (Frontal, Temporal, Parietal, Central, and Occipital); 2) relationships between EC and volumetrics; 3) relationships between EC and HRV. A Two-sided t-test and spearman's correlation were used for statistics and $p<0.05$ was considered significant. Connectivity analysis in the alpha frequency band (8-12 Hz) shows: 1) CH-PATS presented significantly greater EC in the occipital region than in CH-NATs ($p=0.008$) (Figure 1 (A, C)). 2) CH-PATS presented a significant positive correlation between frontal EC and left middle temporal intracranial volume (Icv) ($r = 0.465$, $p = 0.015$), temporal EC and frontal lobe total (Icv) ($r = 0.449$, $p = 0.019$), and temporal EC and Fusiform Total Volume ($r = 0.426$, $p = 0.027$), meaning higher EC related to greater volumes. Conversely, CH-NATS showed significant negative correlations between frontal EC and amygdala (Icv) (r =

- 0.465, p = 0.045), frontal EC with hippocampus (Icv) (r = - 0.623, p = 0.004). 3) In addition, the CH-PATS demonstrated a positive correlation between frontal EC and RMSSD (r = 0.446, p = 0.042), supporting higher EC related to greater HRV, which was not seen in CH-NATs. Our results demonstrate that the A/T pathology was accompanied by enhanced RS-EC in the occipital cortex in CH stage; In CH-PATs, higher frontal or temporal EC was related to higher volumes of temporal or frontal lobe, and higher HRV, supporting a potential compensation mechanism. The results highlight the RS-EC signatures as potential biomarkers for the detection of early AD pathology in CH stage.

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Poster

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Topic: H.04. Executive Functions

Support: FWF Erwin Schrödinger Fellowship J4580
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Title: Supra-modal beta rhythms track contextually relevant information

Authors: *E. EL RASSI[1], C. GRET[1], A. AUMEISTERE[1], S. HAEGENS[1,2,3];
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Abstract: Despite their involvement in many cognitive functions, beta oscillations are among the least understood brain rhythms. Reports on whether the functional role of beta is primarily inhibitory or excitatory have been contradictory. Our framework attempts to reconcile these findings and proposes that several beta rhythms co-exist at different frequencies. It is so far underappreciated that beta could influence behavior by shifting in frequency. In this magnetoencephalography experiment, 32 human participants performed a perceptual discrimination task where they reported which of two sequential auditory or tactile stimuli vibrated faster. We found that changes in beta power and frequency in auditory cortex and motor cortex could predict behavioral outcomes. Our results imply that the analysis of beta oscillations requires caution as beta dynamics are multifaceted phenomena, and that several dynamics must be taken into account to reconcile mixed findings in the literature.

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Poster

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Topic: H.04. Executive Functions

Support: 1R56AG060052-01 (U.S. NIH Grant/Contract)

Title: Effects of Working Memory Training on Task-related Functional Connectivity of Cognitive and Somatosensory Networks

Authors: *P. SKOLASINSKA, E. T. SMITH, C. BASAK;
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Abstract: Large-scale brain networks of older adults are flexible, showing changes in both resting-state (rsFC) and task-related functional connectivity (taskFC) following cognitive training (Lampit et al., 2015; Iordan et al., 2020). Increased taskFC between cognitive networks is shown to support performance of demanding cognitive control tasks (Finc et al., 2020). This study presents secondary analyses of the Phase I randomized clinical trial (NCT03988829) aimed at comparing the effects of an adaptive working memory training requiring higher cognitive control / unpredictable switching (HighC) and similar training requiring lower cognitive control / predictable switching (LowC). In the current study, we investigated the effects of LowC or HighC training on taskFC. We used the whole brain seed-to-voxel approach to identify the brain regions whose taskFC increased or decreased in relation to hub regions of large-scale networks. TaskFC was assessed during performance of the random n-back task with trained (bird) and untrained (digits) stimuli in healthy older adults. The random n-back fMRI task consisted of three 5 min runs of six 40 s task blocks interleaved with seven fixation blocks of 6 s. The blocks had a memory load increasing from 0-back to 2-back to 3-back. The presented stimuli were either pictures of birds (trained) or digits (untrained). Each block consisted of twenty 1.5 s trials. fMRI images were acquired using a slice accelerated multiband EPI sequence with TR/TE = 500/30 ms. Complete pre-training and post-training neuroimaging fMRI data of 28 adults (LowC: N=13, HighC: N=15) were available. We found changes in taskFC between the hubs of the salience network, that is left and right fronto-insular cortex (FIC), and regions of the cognitive and somatosensory networks. There was increased integration between the right FIC and left frontal pole, as well as between left FIC and the right temporal occipital fusiform cortex. Increased segregation was found between right FIC and the right postcentral gyrus and occipital pole as well as between left FIC and the left and right somatomotor regions. No changes in taskFC were identified for FPN and DMN hubs. The results suggest greater increases in taskFC between the cognitive networks, and more segregation between cognitive and somatosensory networks following HighC compared to LowC, and for the trained task rather than the untrained task. Cognitive-somatosensory segregation after HighC training might indicate efficient motor and visual processing on the trained task while increased cognitive network integration might support cognitive control.

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Poster

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Title: Causal evidence for hierarchical predictive coding among cingulo-opercular and frontoparietal networks supporting cognitive control

Authors: *J. WOOD, A. MEYER, D. E. NEE;
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Abstract: Cognitive control is the ability to align behaviors with goals when habit will not suffice. Control engages the frontoparietal (FPN) and cingulo-opercular (CON) networks in humans. Within both networks, distinct sub-systems can be organized along a present/external to future/internal axis from sensorimotor-proximal to sensorimotor-distal areas (Nee, 2021; Wood & Nee, 2023). We have hypothesized this organization allows for temporally organized cognitive control. However, how these networks and sub-systems interact to support this organization remains unclear. One class of models posits CON areas motivate FPN areas to engage control (Botvinick et al., 2001; Menon & Uddin, 2010; Shenhav et al., 2013). Yet other models focus on the reciprocal interactions among the CON and FPN for hierarchical computing of predictions that guide control (Alexander & Brown, 2018). Here, we sought to adjudicate amongst these models by causally perturbing the FPN and examining the impact on the FPN and CON. 34 young, healthy adults performed a task designed to contrast present/externally oriented and future/internally oriented control (Nee & D'Esposito, 2016) during functional MRI (fMRI). Continuous theta burst stimulation (cTBS) was administered to individualized functional, and anatomically defined targets followed by task-based fMRI in a counter-balanced, cross-over design. cTBS was used as a causal probe of effective connectivity with the reasoning that cTBS would primarily impact efferent, but not afferent connections (Bergmann & Hartwigsen, 2021). If the CON acts primarily as a motivator to the FPN, we predicted FPN-cTBS would impact the FPN, but not the CON. By contrast, if reciprocal FPN-CON interactions support prediction computation, disruption of the FPN would cause prediction errors and increased CON activations. Moreover, if FPN and CON areas are arranged hierarchically, prediction errors would propagate throughout the FPN and CON. cTBS was administered to two areas involved in future oriented control: the lateral frontal pole (FPl) and mid-dorsolateral prefrontal cortex (mid-DLPFC), as well as a control site (S1). We found during the future oriented task, mid-DLPFC-cTBS produced increased activations throughout both the CON and FPN. Interestingly, these increases were least pronounced in the targeted future oriented FPN sub-system but were significant in all other network/sub-system pairs. These data demonstrate disruption of a sub-

system leads to prediction errors which propagate across networks and sub-systems. These results suggest temporally organized cognitive control can be understood from a framework of hierarchical predictive coding.

Disclosures: J. Wood: None. **A. Meyer:** None. **D.E. Nee:** None.

Poster

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ONR N00014-17-1-2304

Title: Connectome Fingerprinting Predicts Prefrontal Cognitive Control Activation During Abstract Reasoning

Authors: *K. ISENBURG[1], Y. LIU[2], T. M. MORIN[3], C. E. STERN[1];
[2]Psychology, [1]Boston Univ., Boston, MA; [3]MGH Martinos & Brandeis Univ. Psychology, Boston, MA

Abstract: Recently, machine-learning approaches have been implemented to reliably predict an individual's task-based activity patterns from their resting state functional connectivity, a technique known as "connectome fingerprinting" (CF) (Passingham & Wise 2012, Mars et al. 2018, Tobyne et al 2018, Osher et al. 2019, Finn et al. 2015). These methods could be particularly useful in examining individual differences during higher-order cognitive tasks, such as abstract reasoning. Previously, our group developed a simplified version of the Raven's Progressive Matrices task for use during functional Magnetic Resonance Imaging (fMRI). During the task frontoparietal brain regions in the cognitive control network (CCN) showed increased activity associated with symbolic reasoning (Morin et al. 2023). In the current study, we hypothesized that when compared to the group average map of task activation, an individual's CF would better predict individual brain activation patterns in the lateral prefrontal cortex (lPFC) of the CCN during a symbolic reasoning task. We chose this region based on its task activation during our previous study and its involvement in both working memory and abstract rule encoding processes (Funahashi et al. 1989, Wallis et al. 2021). We used the Schaefer 400 parcellation of the Yeo 7 network atlas (Yeo et al. 2011, Schaefer et al. 2018) to define the lPFC and CF ROIs. We implemented a nested leave-one-out, penalized-based ridge regression method based on the implementation by Tobyne et al. 2018, to predict brain activity associated with symbolic reasoning based on subjects' CF. We show that CFs are a better at predictor of subject-specific task activation in the lPFC (left hemisphere: r= 0.51, right

hemisphere: r= 0.52) compared to the standard general linear model group-average (left hemisphere: r=0.31, right hemisphere: r=0.39). This difference was statistically significant for both hemispheres (left: p=0.00004, right: p=0.0009). This result suggests that the CF may provide a more accurate model in predicting individual-level task activation during fMRI. Further, we show that CF methods can be used in tasks that measure higher order cognitive processes such as abstract reasoning.

Disclosures: **K. Isenburg:** None. **Y. Liu:** None. **T.M. Morin:** None. **C.E. Stern:** None.

Poster

PSTR299. Network Activity of Executive Functions

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR299.15/UU18

Topic: H.04. Executive Functions

Support: NIH Grant R01MH118370

Title: Individual Variation in Task Signals from a Precision fMRI Dataset

Authors: *N. LABORA[1,2], M. DORN[3], D. M. SMITH[3], A. DWORETSKY[1,2], C. GRATTON[1,2]; [1]Program in Neurosci., [2]Dept. of Psychology, Florida State Univ., Tallahassee, FL; [3]Northwestern Univ., Evanston, IL

Abstract: When completing goal-oriented tasks, humans flexibly configure information processing to meet task demands through control signals related to task initiation, maintenance, and error processing. Past studies have found that these control signals are identified in cingulo-opercular and fronto-parietal brain networks across multiple tasks. However, to date, a relatively unexamined question is whether (and to what extent) task control signals differ across people. In this study, we used a 'precision' fMRI approach which utilizes extended data collection from each individual to examine the characteristics of task signals in individuals. The dataset includes data from N = 34 participants (24 F, ages = 18-35), each with ~9 hours of MRI data, including resting-state fMRI and 40 min. per 3 mixed block event-related designs: a visual rhyming word task, an auditory abstract/concrete word judgement task, and a visual mental rotation task. Using a general linear model with finite-impulse-response coding of events, we obtained estimates for correct and error signals and their contrast in each task, for each participant across sessions. These signals were compared across participants, tasks, and split-half sessions using spatial correlation. In all cases, activation map similarities were largest for within-subject/within-task comparisons, followed by within-subject/across-task, across-subject/within-task, and finally across-subject/across task. The consistency across tasks was amplified when limited to the cingulo-opercular and fronto-parietal control networks, but strong differences across individuals remained. These results were consistent across nearly all participants and indicate a large effect of individual variation on correct and error trial activity, as well as within their differences. This large individual variation effect has strong implications for the study of task control signals, and

contributes to the growing body of evidence for the value of examining subject data at the individual level.

Disclosures: **N. Labora:** None. **M. Dorn:** None. **D.M. Smith:** None. **A. Dworetsky:** None. **C. Gratton:** None.

Poster

PSTR299. Network Activity of Executive Functions

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Topic: H.04. Executive Functions

Support: NIH grant T32 NS047987
NIH grant R01MH118370
NIA grant P30AG13854

Title: Investigating individual differences in aging networks: a Precision fMRI dataset in older adults

Authors: *D. C. PEREZ RIVERA[1], G. WULFEKUHLE[2], J. J. HERNANDEZ[1], G. TRAN[1], E. M. GORDON[4], C. GRATTON[3];
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Abstract: Understanding the changes in brain networks associated with aging is crucial in neuroscience. Aging is associated with cognitive decline, but with substantial variability in cognitive performance and brain measurements across individuals. In this study, we present a dataset of extended fMRI measurements in a small cohort of older adults (N = 8, ages = 65-75). Our objective is to provide a benchmark for the reliability and stability of precision fMRI in older adults, and to explore individual differences in brain networks in the context of aging. The dataset includes 96-231 minutes of low-motion resting-state functional connectivity (rs-FC) data per cognitively healthy individual. Preliminary results indicate that precision measurements of rs-FC in older adults achieve high reliability ($r > .85$) with an average of 50 minutes of data. While younger adults reach this level of reliability with significantly less data ($p < 0.02$), with sufficient data, older and younger adults do not differ significantly in their peak reliability. Measurements of older adults are stable across sessions, though older adults are moderately less stable than younger adults ($p < 0.04$). Interestingly, older adults exhibit increased inter-individual variability compared to young adults ($p < 0.001$), primarily driven by association networks. This finding underscores the importance of studying brain network variation in aging. We propose three potential applications of precision data for the study of brain aging. First, our analyses suggest that more data (~40 minutes) is needed to produce reliable and unbiased measurements of network properties like segregation. Second, we show that precision data can be used to create individualized parcellations of the cortical surface, revealing substantial variability in brain

network organization across individuals. Third, we demonstrate that precision data can be used to find localized regions where individuals differ substantially from the group average rs-FC patterns. These analyses highlight the importance of leveraging modern methods to study brain network variation in aging, improving our understanding of cognitive heterogeneity. Precision fMRI in older adults provides a comprehensive platform to investigate individual differences in brain networks during aging, enhancing our knowledge of individual trajectories of brain health and facilitating the development of precision medicine for age-related cognitive disorders.

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Poster

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Topic: H.04. Executive Functions

Support: NIH R01MH118370
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Title: A characterization of connector hub brain regions across individuals

Authors: *G. WULFEKUHLE[1], D. C. PEREZ RIVERA[3], Z. LADWIG[4], A. DWORETSKY[1], E. M. GORDON[5], C. GRATTON[1,2];
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Abstract: The brain is organized into discrete systems, or networks, which exhibit correlated activity during fMRI, a technique termed functional connectivity (FC). Interactions between networks are aided by “connector hubs” or regions of the brain that have links to multiple networks. Studies have emphasized the importance of hubs in facilitating cognitive processes and maintaining network organization. Hubs can be identified using the participation coefficient (PC) metric which quantifies the distribution of a node's connections across different networks. Most prior work has calculated PC based on group-average fMRI data. However, given recent reports of large individual differences in brain networks, this approach may hide idiosyncratic hubs. Here, we used data from the Midnight Scan Club dataset (N = 9, F = 4, ages = 24-34) to locate individual and group hubs and characterize their properties. We identified hub regions by computing PC for individualized parcellations of the cortex. Parcels with a PC value in the top 20 percent were marked as hubs. PC was calculated using individual and group-average fMRI data. Additionally, all the individual PC maps were averaged to create an “overlay” map. When compared, the group PC map had an average r = .2 (range = .16-.23) to each individual’s PC map, while the overlay PC map an average r = .53 (range = .49-.57) to each individual’s PC map.

We also found a large proportion of hubs in regions of each individual's PC map that did not show hub representations in the group or overlay maps; while some regions were adjacent to group and overlay hubs and had similar connectivity patterns, others were more unique. Future directions include examining how group and individual hubs in young adults compare to older adults. The current data suggests that some connector hubs are shared across individuals, but that there is a large proportion of individual-specific hub regions. The prevalence of idiosyncratic hubs demonstrates the importance of looking at individualized data.

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Poster

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Title: Two distinct forms of functional network variants in the human brain

Authors: *A. DWORETSKY[1,3,9], B. A. SEITZMAN[4], B. ADEYEMO[5], A. N. NIELSEN[5], A. S. HATOUM[6], D. M. SMITH[11,9], T. E. NICHOLS[12,13], M. NETA[14], S. E. PETERSEN[3,5,6,7,8], C. GRATTON[1,2,9,10];
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Abstract: The organization of the human brain into large-scale functional networks has been well-validated at the group level. However, recent work using resting-state functional MRI (fMRI) has revealed locations of idiosyncratic, individual-specific differences in functional network organization. Focal regions with the strongest individual variation, termed "network variants," have been shown to be common, stable across task states, and related to behavior.

Here, we further investigate the properties of network variants by classifying them into two forms: (1) "border shift" variants which represent proximal, spatially contiguous extensions of an individual's network boundary relative to a group-average, and (2) "ectopic intrusions," which appear as distal, spatially unconnected functional network changes in an individual relative to the group. Using data from highly sampled individuals in the Midnight Scan Club (N=9) and Human Connectome Project (N=823) datasets, we demonstrate that border and ectopic variants differ in their spatial distributions across the cortex and in their relative frequency of association with functional networks. Additionally, in both datasets, we show that border and ectopic variants exhibit shifted task responses: in a large set of task contrasts, we demonstrate that border and ectopic variants show shifted activations relative to the group-average networks, with border variants' activations more closely approximating their attributed functional network than ectopic variants. Further, we investigated the relationship between genetics and network variant location: while both forms of variants show evidence of heritability, border variants are more similar than ectopic variants among pairs of identical twins. We find that both forms of variants can be used to cluster individuals into groups based on their functional network affiliations, but border and ectopic variants produce categorically different sub-groups. Finally, exploratory analyses show that border and ectopic variants predict different behavioral phenotypes to a small degree. Together, these findings provide evidence for two separable forms of network variants, with different network properties and links to genetics and behavior, bolstering the need for further discussion on how to properly account for various types of individual differences in studies of cortical system organization.

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Poster

PSTR299. Network Activity of Executive Functions

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Program #/Poster #: PSTR299.19/UU22

Topic: H.06. Social Cognition

Support: NIH Grant R01 MH131664

Title: Mapping semantic representations in animals and humans at single-cell resolution

Authors: I. CAPRARA[1], ***M. JAMALI**[1], B. MASH[1], M. MUSTROPH[2], B. L. GRANNAN[3], W. MUNOZ MIRANDA[1], D. MESZENA[1], A. PAULK[4], S. S. CASH[5], R. BÁEZ-MENDOZA[6], Z. WILLIAMS[1];
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Abstract: Many animals, including humans, are thought to share conserved neural mechanisms for processing semantic information, which serve as a common foundation by which to navigate their respective environments. While prior comparative studies have shed important light on neuroanatomical similarities across animal species, understanding whether and to what degree semantic information may be similarly represented by neurons has remained a significant challenge. Here, we aimed to begin addressing these questions by performing single-neuronal recordings in both monkeys and humans in a homologous prefrontal area previously shown to be involved in semantic processing and categorization. To further allow for comparison, we presented similar sets of images that varied broadly in semantic content, valence and theme and which could be commonly compared across species. We also included normative ratings of the images using a Mechanical Turk, cross-modal testing across distinct stimuli and behavioral validation to confirm their salience and generalizability. By creating vectorial representations of each stimulus and by employing a combination of single-neuronal and population analyses, we find that many of the neurons in both monkeys and humans responded selectivity to specific semantic domains and that their population activities could be used to decode categorical information about the image being presented. We find, however, a wide range in how semantic information is represented within neuronal ensemble across species and how the stimuli mapped across the population's response patterns - with striking similarities in the relationships between certain semantic domains and their hierarchical organization. Together, these findings reveal a detailed cellular representation of semantic information in the prefrontal cortex of monkeys and humans and begin to identify the core semantic manifolds that may be shared across animal species.

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Poster

PSTR300. Central and Prefrontal Mechanisms II

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Program #/Poster #: PSTR300.01/UU23

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Natural Science Foundation of China 31871132

Title: Rational use of limited resources for compositionality in sequence working memory in macaque prefrontal cortex

Authors: *S. LI[1], J. CHEN[1], Y. XIE[2], L. WANG[1];
[1]Inst. of Neuroscience, CAS Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China; [2]Lingang Lab., Shanghai, China

Abstract: Our brain is remarkably limited in how many items it can hold simultaneously, but it can also represent unbounded novel items through compositional generalization. However, at the neural level, how the brain represents and optimally uses the limited resources in working memory (WM) remains unknown. Here, we investigated the neural mechanisms of sequence working memory (SWM) resources using two-photon calcium imaging and high-throughput electrophysiological recordings to record thousands of neurons in the prefrontal cortex (PFC) of macaque monkeys performing a delayed-sequence-reproduction task. We found the geometry of SWM in PFC neural states exhibiting a compositional code with generalizable and separate low-dimensional rank subspaces. SWM capacity is not fixed by the number of items but rather is a limited resource characterized by neural population activity shared rationally between ranks. Crucially, this rational use of resources is determined by the compositionality of SWM, such that the responses of each neuron allocated among items depend on the geometry of associated rank subspaces. The neural encoding strength in each rank subspace, resulting from the proportion of resources allocated, faithfully predicted the precision of remembered items and their capacities in monkeys' behavior. Thus, the geometry of compositionality underlies the rational use of limited resources in SWM.

Disclosures: S. Li: None. **J. Chen:** None. **Y. Xie:** None. **L. Wang:** None.

Poster

PSTR300. Central and Prefrontal Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR300.02/UU24

Topic: H.05. Working Memory

Title: Relationships between frontal lobe hemodynamics and working memory task performance.

Authors: *J. E. KOCH, H. A. JACQUEZ;
Psychology, Univ. of WI Oshkosh, Oshkosh, WI

Abstract: Links between frontal cortex activity and cognitive task performance can be revealed by numerous available imaging techniques, one of which is functional near infrared spectroscopy (fNIRS) that detects levels of oxygenated (HbO) and deoxygenated hemoglobin in cortical (PFC) areas. In this exploratory study, college-aged participants (N = 27) completed six computer-based working memory tasks of varying difficulty (three n-backs, detection, 1-card learning, and maze completion) while fNIRS HbO data were collected. Performance accuracy decreased

systematically and significantly across tasks as difficulty increased, but task-related differences in HbO levels were less consistent and were found only at fNIRS optode 15. In addition, the maze task produced a wide array of performance results with little effect on changes in optode 15 HbO levels from baseline. Regression analyses of individual task performance and their respective optode 15 HbO levels revealed inverse relationships in four of the six tasks, the strongest being found during the 2-back task and the weakest during tasks for which performance ceiling effects existed. These results complement similar research demonstrating relationships between cognitive task difficulty and changes in frontal lobe hemodynamics and contribute to the growing body of research on fNIRS and frontal lobe-based performance capabilities involving working memory, including the potential for using fNIRS data to predict performance on these and similar tasks.

Disclosures: J.E. Koch: None. **H.A. Jacquez:** None.

Poster

PSTR300. Central and Prefrontal Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR300.03/UU25

Topic: H.05. Working Memory

Title: Mesoscale modules for the control of working memory in primate frontoparietal cortex

Authors: *X. WANG[1,2], D. HÄHNKE[3], S. N. JACOB[3];
[1]Dept. of Neurosurgery, Technische Univ. München, Munich, Germany; [2]Grad. Sch. of Systemic Neurosciences, Ludwig-Maximilians-Universität München, Munich, Germany; [3]Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany

Abstract: Working memory tasks often reveal sustained neural activity that represents the memorized information. However, recent discoveries suggest an alternative biophysical model with temporally sparse, short-lived oscillatory activity arranged in bursts. How these oscillatory bursts relate to the functional organization of local and long-range circuits in the working memory network and the storage and processing of working memory content remains unclear. To address these questions, we recorded spiking activity and local field potentials (LFP) in the lateral prefrontal cortex (PFC) and ventral intraparietal area (VIP) of two rhesus monkeys performing a delayed-match-to-sample task with visually presented target numerosities (sets of dots) and interfering distractor numerosities. We analyzed the spatiotemporal patterns of LFP bursts across recording sites and their relationship to neuronal spiking activity. We found that the burst probability was monotonically modulated by numerosity, while individual neurons typically showed peaked tuning to number. In both brain regions, bursts of different frequencies exhibited unique patterns during different task epochs. In PFC, where precise reconstruction of the spatial layout of recording sites was possible, sensory signals triggered by sample presentation arrived at separate anterior sites, associated with either gamma (60-90Hz) or beta (15-35Hz) band oscillations. Sample memory maintenance was accompanied by gamma bursts at

a more posterior site. Remarkably, following distraction, sample information was recovered in the same posterior sites, albeit with beta bursts dominating. Local and inter-regional functional connectivity differed across these prefrontal clusters, further supporting their distinct roles in working memory processing. These mesoscale modules remained spatially stable across recording days. Our findings indicate that LFP bursts in the frontoparietal cortex are not direct representations of working memory content. Instead, frequency-specific oscillatory neural activity contributes to contextual processing and dynamic organization within a distributed cortical network. Spatially separable modules in the prefrontal cortical sheet are tasked with sensory and memory coding. Our study sheds light on the complexity of working memory mechanisms and circuit organization in frontoparietal cortex, emphasizing the importance of considering mesoscale spatiotemporal dynamics in future research.

Disclosures: X. Wang: None. **D. Hähnke:** None. **S.N. Jacob:** None.

Poster

PSTR300. Central and Prefrontal Mechanisms II

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Program #/Poster #: PSTR300.04/UU26

Topic: H.05. Working Memory

Support: NIH R01MH115042

Title: Context dependent changes in neural representation of working memory

Authors: *M. UCHIMURA[1], M. PANICHELLO[3], T. BUSCHMAN[2];
[2]Princeton, [1]Princeton Univ., Princeton, NJ; [3]Stanford Univ., Palo Alto, CA

Abstract: Working memory is central to cognition, allowing one to hold items ‘in mind’. However, despite its importance, working memory is faulty - stimuli are imperfectly encoded in memory and memories can degrade over time. Previous psychophysical studies suggest the accuracy of memories depends on the context. Memories are inaccurate when there is a large range of stimuli that could be remembered on any given trial. However, when the range of stimuli is smaller, memories are more accurate. This suggests working memory representations are adaptable, changing to efficiently store information in working memory for the current context. To understand the neural mechanisms that support this adaptability, we trained two monkeys to perform a working memory task that required them to remember two colored squares and, then, after a memory delay, report the color of the ‘selected’ memory. Initially, the color of each stimulus was randomly selected from the full color wheel (i.e., the entire rainbow). However, after a few hundred trials, the stimuli colors were drawn from one half color space (arbitrarily chosen). Consistent with previous work, the monkeys were more accurate when colors were drawn from a smaller range of possible values (the half color space). In addition, we found the monkey’s response was attracted towards the center of restricted range, reducing the accrual of errors over time. To understand the neural basis of these improvements, we

simultaneously recorded from prefrontal and parietal cortex as the monkeys performed the task. The distance in neural space of the representation of nearby colors was greater when the color range was restricted. Furthermore, the geometry of the color representation changed from semi circular to triangular, allowing nearby colors to be more finely discriminated and, thus, improving working memory accuracy. Our results provide insight into how neural representations adapt to the context in order to improve working memory accuracy.

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Poster

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Program #/Poster #: PSTR300.05/UU27

Topic: H.05. Working Memory

Support: Natural Science Foundation of China 31871132

Title: Flexible control of sequence working memory in macaque frontal cortex

Authors: *J. CHEN[1], C. ZHANG[1], P. HU[1], Y. XIE[2], B. MIN[3], L. WANG[1];
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Abstract: To memorize a sequence, one must serially bind each item to its order. In this process, how the brain flexibly controls a given input to its associated order in sequence working memory (SWM) remains unknown. Here, we trained two macaque monkeys to perform a delayed sequence-sorting task. Monkeys had to memorize and reproduce spatial sequences of random length (length 1, 2, or 3) using different sorting algorithms, either in the presented order (forward task) or in the reverse order (backward task). We investigated the neural representations of the SWM control process by conducting high-throughput electrophysiological recordings, capturing activity from thousands of neurons in the frontal cortex. We employed a task subspace decomposition framework to break down the high-dimensional neural state space into smaller, task-relevant subspaces while adaptively determining when the representation of task-related variables appears in each subspace. We found separate representations of sensory and SWM at the population level within the same frontal circuitry, reflecting the control process through their organized neural dynamics. Item at each rank was sequentially entered into a common entry subspace and, depending on the sorting algorithm, flexibly and timely controlled into their associated rank-selective SWM subspaces. Crucially, neural activities in these subspaces can faithfully predict monkeys' behavior in single trials. Thus, well-orchestrated neural dynamics in the frontal cortex underlie the flexible control of SWM.

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Poster

PSTR300. Central and Prefrontal Mechanisms II

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Program #/Poster #: PSTR300.06/UU28

Topic: H.05. Working Memory

Support: NIH EY026924
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Research to Prevent Blindness

Title: Optogenetic Manipulation of V4 to FEF Projections during Working Memory

Authors: *P. COMEAUX[1], L. NURMINEN[2], F. FEDERER[1], A. ANGELUCCI[1], B. NOUDOOST[1];
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Abstract: Working memory (WM) is the cognitive ability that allows an organism to maintain recent information in order to guide behavior. Communication between the sensory areas that process visual information and prefrontal areas that prepare plans of action is pivotal to the information flow during WM tasks, and the efficacy of this communication has been shown to depend on the content of WM. Moreover, coherence between prefrontal and posterior visual areas has been shown to correlate with success in WM tasks. We tested whether local oscillations within prefrontal cortex and coherent oscillations between this area and visual areas determine the efficacy of inputs arriving in prefrontal cortex. We injected an anterograde viral vector expressing channelrhodopsin-2 into rhesus macaque V4. After allowing viral expression in V4 axon terminals, we performed photostimulation within the Frontal Eye Field (FEF) to stimulate V4 axon terminals. Photostimulation was performed during a classic memory guided saccade (MGS) task and during a modified MGS task with a visual distractor. We recorded local field potentials and spiking activity within both regions. We found that the efficacy of V4 inputs to drive FEF spiking activity depends on oscillation phase within FEF. Moreover, we found evidence that the excitation of V4 axon terminals within the FEF can bias WM-guided behavior. We present the analysis regarding the role of oscillatory phase within FEF, as well as the relationship between FEF and V4 oscillations, in gating the efficacy of V4 inputs to FEF. This approach for causal manipulation of projection-specific pathways between FEF and V4 during WM will enable us to characterize the factors affecting the dynamic gating of information transmission and how this flexible gating can serve as a basis for privileged processing of behavioral targets.

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Poster

PSTR300. Central and Prefrontal Mechanisms II

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Topic: H.05. Working Memory

Support: NIH MH093354

Title: Nicotinic a7 receptor interacting with muscarinic M1 receptor enhances working memory related activity in primate dorsolateral prefrontal cortex

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Abstract: Acetylcholine (Ach) plays an important role in the cognitive function of the prefrontal cortex (PFC) through both ionotropic nicotinic and metabotropic muscarinic receptors. Our previous studies have revealed both α7 nicotinic acetylcholine receptors (α7-nAChR) and muscarinic M1 acetylcholine receptors (M1R) are localized in dorsolateral PFC (dlPFC) glutamatergic-like synapses. The stimulation of α7-nAChR or M1R enhances working memory related activity of Delay cells in primate dlPFC, and is permissive for NMDAR actions, rescuing neuronal firing from NMDAR blockade. However, over-stimulation of α7-nAChR may cause receptor desensitization and over-stimulation of M1R may hyperpolarize the membrane through PKC-cAMP-PKA signaling. Indeed, physiological studies found that over-stimulation of either α7-nAChR or M1R reduced working memory related activity and impaired working memory function, potentially limiting clinical utility. We hypothesize that the Delay cells may respond to both of M1R and α7-nAChR stimulations, thus, combined low-dose stimulation of M1R and α7-nAChR will synergize to greatly enhance Delay cell firing. In this study, we iontophoretically applied low doses of the α7-nAChR agonist PHA 543613 (PHA) and the M1R positive allosteric modulator VU 0357017 (VU) to Delay cells in primate dlPFC as monkeys performed an oculomotor delayed response task. Our data show that the same dlPFC neuron can respond to both of M1R and α7-nAChR stimulations. Co-application of low dose of VU and PHA showed synergistic enhancing effects on delay firing. These data suggest that low-dose stimulation of multiple cholinergic receptors could be a potential treatment strategy to boost PFC cognition under conditions of reduced cholinergic signaling.

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Poster

PSTR300. Central and Prefrontal Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR300.08/VV2

Topic: H.05. Working Memory

Support: NIH Grant RF1 AG060778

Title: Optogenetic investigation of medial prefrontal cortical contributions to delayed response working memory performance in young and aged rats

Authors: *L. CAO[1], M. FARAJI[1], C. HERNANDEZ[4], K. GONZALEZ[2], C. C. LABISTE[2], A.-R. WHEELER[2], N. G. WRIGHT[2], S. M. BETZHOLD[2], C. FRAZIER[3], B. SETLOW[1], J. L. BIZON[2];
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Abstract: Changes within the medial prefrontal cortex (mPFC) are associated with age-related cognitive impairments including deficits in working memory. Working memory, the ability to retain information over a relatively brief delay, is known to involve the mPFC as shown by lesions and pharmacological manipulations. Such studies do not demonstrate how the mPFC specifically contributes to temporally-discrete phases of working memory (acquisition, maintenance, and retrieval), however, nor is it known whether mPFC contributions to these distinct phases changes across the lifespan. To address these questions, we optogenetically activated or inactivated pyramidal neurons within the mPFC of male young adult and aged rats to dissect the role of the mPFC during distinct phases of working memory. Young adult (6 mo.) and aged (24 mo.) male Fischer 344 x Brown Norway F1 hybrid rats were surgically implanted with bilateral guide cannulae targeting the mPFC, through which AAVs encoding halorhodopsin, channelrhodopsin, or a control construct were delivered and optic fibers were implanted. Rats were subsequently trained in operant chambers in a three-stage delayed response working memory task. On each trial in this task, rats were presented with a sample lever (either left or right), a press on which initiated a delay phase ranging from 0-24 s. After the delay expired, both levers were extended, and rats had to choose the same lever pressed during the sample phase in order to earn a food reward. Rats were trained until reaching stable baseline performance, at which point they received laser light of the appropriate wavelength delivered to the mPFC. Aged rats showed impaired task accuracy relative to young under baseline conditions. Inactivation of mPFC during the sample phase impaired accuracy in both age groups, particularly at longer delays. In contrast, mPFC inactivation during the choice phase enhanced accuracy at the longest delay, particularly in aged rats. Surprisingly, neither inactivation nor activation affected accuracy in either age group. The results suggest that the mPFC plays temporally distinct roles in working memory, but that its contributions may differ across the lifespan.

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Poster

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Program #/Poster #: PSTR300.09/VV3

Topic: H.05. Working Memory

Support: NSF NeuroNex Grant 2015276

Title: Flexible neuromodulation of synaptic strengths via electrical shunting in dorsolateral prefrontal cortical dendritic spines

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Abstract: Prefrontal cortical circuits rely on strong recurrent excitations to sustain representations for working memory and other cognitive functions. Control of effective recurrent strength can endow these circuits with flexibility in their computational and dynamical regimes, and immunoelectron microscopy data, coupled with physiology, of the primate dorsolateral prefrontal cortex (dlPFC) suggests this may involve key molecular actions on dendritic spines which receive excitatory connections. The specific functions of spines has been debated for decades as either being purely biochemical, where calcium gradients support synaptic plasticity, or electrical, where spines function as electrical compartments that modify synaptic potentials. Recent experiments have established that spines are indeed electrically isolated from parent dendrites and capable of activating independently in subthreshold potentials. Spines in layer III of dlPFC have also been shown to contain complex molecular machinery where neuromodulators (e.g. acetylcholine, noradrenaline, dopamine) via feedforward cAMP-calcium signaling can alter the open state of potassium channels on spines, dynamically altering network connection strength (Dynamic Network Connectivity). Here, we examined through multiscale computational modeling how experimentally-constrained electric compartmentalization can be a mechanism for such neuromodulatory effects to control the regime of a cortical circuit's effective recurrence. First we simulate a spatial neuron model with a single spine on a dendrite and a minimal set of channels to study how voltage-dependent calcium feedback loops and calcium-dependent potassium channels in spines can modify somatic synaptic potentials, via electrical shunting at high-resistance spine necks. Phenomenological fitting to capture synaptic strength dependence on neuromodulation can then be embedded in spiking network models of attractor dynamics supporting working memory. Spine-based control of recurrent strength can shift a network's operating regime, from robust working memory that resists distractors, to distractible working memory, to putting the circuit "off-line" for externally-driven behavior. These multiscale modeling results establish the feasibility of rapid reconfiguration of recurrence in prefrontal circuits by neuromodulation, identify computational functions of dendritic spines, provide testable predictions for future experiments, and inform future neural circuit models of cognitive function.

Disclosures: H. Cho: None. **J.D. Murray:** None. **A.F. Arnsten:** None.

Poster

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Program #/Poster #: PSTR300.10/VV4

Topic: H.05. Working Memory

Support: NIH R01 EY019041
DOD VBFF

Title: Parallel representation of visual, saccadic, and abstract working memory signals in FEF and LIP

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Abstract: In primates, neuronal activity in cortical oculomotor networks encodes a diverse array of variables relevant for visually-guided behavior — among others, the location and features of visual stimuli, information in working memory (WM), abstract decision variables, and the targets of intended or ongoing eye movements. To study how these visual, WM, and saccadic signals interact, we designed a task that requires animals to make eye movements to visual targets that are alternately informed by or independent of abstract category information in WM. One monkey (*Macaca mulatta,* 10kg) was trained to classify a motion stimulus (100% coherence; 1 of 6 directions) into one of two categories, indicated by an eye movement to an associated color target after a 1s delay. On some trials, the animal was also instructed during the delay to make a category-independent eye movement to a salient peripheral target (1 of 4 locations, chosen at random). This design requires the animal to remember information about the abstract category of the sample stimulus while also planning and executing saccades. We used multiple linear electrode arrays to record from neuronal populations in the frontal eye fields (FEF; 7 sessions, mean=58 units/session), lateral intraparietal area (LIP; 11 sessions; mean=80 units/session), and lateral prefrontal cortex (LPFC; 8 sessions; mean=111 units/session) during task performance (82.5 ± 10.6% correct, mean ± s.d. across sessions). Spiking activity of units in both regions was significantly modulated by visual target presentation, saccade preparation/execution, and stimulus category (target location: 295/411 units (FEF), 463/880 units (LIP); stimulus category: 185/411 units (FEF), 471/880 units (LIP); for each variable, Kruskal-Wallis test, significance at $P < 0.05$). State-space and decoding analyses of neural population activity in FEF on single trials show that saccade targets and WM content are represented simultaneously. During instructed category-independent eye movements made in the delay, FEF activity separately encoded both the currently-relevant target's location and the remembered, but currently-irrelevant, category (logistic regression from single trials' activity, averaged through time; category: 82.0 ± 6.8% cross-validated accuracy, chance=50.4 ± 0.3%; saccade target location: 63.5 ± 14.8% cross-validated accuracy, chance=25.5 ± 0.4%; mean ± s.d. across sessions). Ongoing data analyses aim to clarify further how neural populations in brain regions associated with sensorimotor processing and executive functions integrate and multiplex representations of the distinct variables important for ongoing behavior.

Disclosures: **M. Rosen:** None. **S. David:** None. **D.J. Freedman:** None.

Poster

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Program #/Poster #: PSTR300.11/VV5

Topic: H.05. Working Memory

Support: U19 NS123714

Title: Impact of subcortical inputs on frontal cortex via MD thalamus

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Abstract: The frontal cortex orchestrates complex, high-level behaviors, including action selection, decision-making, and short-term memory. Neural activity in the prefrontal cortex (PFC) is driven by long-range excitatory projections from the mediodorsal thalamus (MD). Communication between the PFC and MD is particularly important for cognition and becomes disrupted in various mental health disorders. While PFC can support activity in MD, the ability of subcortical inputs to impact activity in these thalamocortical loops is unknown. Here, we use retrograde and transcellular viral tracing, electrophysiology, and optogenetics to determine how multiple subcortical inputs engage specific nuclei in MD to influence PFC in the mouse brain. We find that PFC-projecting thalamocortical cells in MD receive distinct inputs from subcortical inputs, including superior colliculus (SC) and ventral pallidum (VP). We show that inputs from SC and VP are anatomically segregated in PFC-projecting MD subdivisions. Lastly, we find that by differentially engaging subdivisions of MD, subcortical inputs influence distinct subregions within the PFC. Together, our findings illustrate how MD route different subcortical signals to influence neural activity in the PFC.

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Poster

PSTR300. Central and Prefrontal Mechanisms II

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Program #/Poster #: PSTR300.12/VV6

Topic: H.05. Working Memory

Support: NSF Neuronex 2015276

Title: Spatial scales of coding for working memory in primate lateral prefrontal cortex

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[3]Neurosci., [4]Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: The prefrontal cortex (PFC) is consistently active during working memory (WM). While non-human primate (NHP) electrophysiology finds that PFC maintains WM representations, these item-related PFC signals are harder to detect with human neuroimaging. This discrepancy may result from spatial intermixing of neurons in PFC with different functional tuning. However, uncovering the functional microcircuitry for WM is difficult without detailed spatial organization about neuronal populations. Here, we leveraged a novel, two-photon calcium imaging dataset in NHPs (Xie et al., Science, 2022) to investigate the functional organization of WM circuits. In a multi-item delayed saccade WM task, 2 or 3 spatial locations were sequentially presented and subjects (N=2) had to reproduce the target locations, in order, after a delay period. During task sessions, calcium traces were recorded from 33 fields-of-view (~500x500μm) in area 9/46 of lateral PFC (~5,300 total cells). We then analyzed the relationship between WM coding and microscale organization. First, neurons closer together in cortical space were more likely to share functional tuning properties for WM locations. However, this pattern of spatial autocorrelation among neurons is much shallower and flatter than the exponential drop-off of spatial autocorrelation among neurons in visual areas, indicating a greater functional mixing of nearby cells in PFC. Second, neurons with the strongest conjunctive/abstract coding - whose spatial tuning changed based on the sequence position in WM - were clustered tightly together at a 100μm scale. Finally, this single-neuron organization also influenced population decoding measures: neural activity spatially averaged at finer scales (25μm) showed stronger WM item representations at position 1 in sequences, but this spatial scale degraded at positions 2 and 3 with increased WM load. The degradation of fine spatial scales of neuronal coding with WM order and load may help reveal a circuit-level bottleneck for fundamental capacity constraints on the WM system. Overall, there is a fine microscale organization of abstract WM coding in PFC likely inaccessible to voxel-level sampling, helping to reconcile discrepancies between human neuroimaging and NHP electrophysiology perspectives of WM coding in PFC.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Topic: H.05. Working Memory

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Simons Foundation Pilot Award 872599SPI

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Scialog Grant 29059

Title: A cholinergic mechanism enabling task-specific computation across the cortex

Authors: *J. LUO[1], P. S. SALVINO[1], A. RAPP[1], S. IBARRA[1], J. CANTON-JOSH[1], R. LU[1], L. PINTO[1,2];
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Abstract: Global activity patterns in the dorsal cortex are reorganized when mice perform perceptual decision-making tasks involving different underlying computations with varying complexity. However, the circuit mechanisms responsible for these large-scale activity changes remain unknown. An interesting possibility is that they involve neuromodulatory input to the cortex. In particular, cholinergic neurons in the basal forebrain project widely across cortical areas while exhibiting topographical and functional heterogeneity. They are therefore well equipped to serve as an orchestrator of task-dependent large-scale cortical activity. To test this hypothesis, we transgenically expressed Cre-dependent GCAMP6s in cholinergic (choline-acetyltransferase-expressing) neurons in mice and imaged cholinergic axonal activity using mesoscale widefield calcium imaging across the entire dorsal cortex. During imaging, the mice performed a cued task-switching paradigm while navigating in virtual reality, with dozens of unpredictable switches within a session. Specifically, they rapidly switched between a complex task that requires evidence accumulation over time and a simple task where the correct choice on each trial is indicated by a salient visual cue. We observed clear task differences in cholinergic activity, which appeared heterogeneous across cortical areas and task epochs. To investigate whether cholinergic input is required for behavioral performance in a task-specific manner, we injected the pan-muscarinic cholinergic antagonist scopolamine or saline prior to behavioral sessions. Strikingly, blocking cholinergic input specifically impaired performance in the complex task while leaving performance in the simple task intact. In addition, muscarinic acetylcholine receptor blockade diminished task differences in cortical excitatory activity and reduced decorrelation across areas in the complex task. These findings suggest that cholinergic input is recruited during perceptual decision-making in a task-dependent manner to shape cognitive computation across the cortex.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Topic: H.05. Working Memory

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Alfred P. Sloan Foundation Grant SP0070621
Scialog Grant 29059

Title: Large-scale cortical dynamics during decision making are shaped by computation timescale

Authors: *R. M. COSTA, *R. COSTA, P. S. SALVINO, J. K. LUO, S. M. IBARRA, L. PINTO;
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Abstract: Behaviors requiring different computations recruit distributed yet distinct cortical dynamics. However, the principles organizing these distributed dynamics are unknown. In particular, the role of computation timescales in the recruitment of cortical dynamics remains untested. To address this gap, we have developed a novel task for mice navigating in virtual reality (VR), termed delayed match-to-evidence (DMTE). This is a variant of delayed match-to-sample, in which the sample is variably noisy and gradually revealed to the mouse, such that it requires evidence accumulation. Thus, the task dissociates in time the computations of evidence accumulation, short-term memory, and choice. Crucially, we also use VR movement gain manipulations to independently and systematically vary the duration of accumulation and memory. Task performance improved with decreased sample noise and increased duration of evidence accumulation, but suffered with increased short-term memory durations. A behavioral logistic regression model showed that sample noise made the largest contribution to performance, closely followed by computation timescales. Importantly, evidence duration and memory duration impacted performance by similar magnitudes but in opposite directions, showing that the DMTE task dissociates computation timescale and computation difficulty. To ask whether computation timescales are a principle guiding the organization of large-scale cortical activity, we are performing mesoscale widefield Ca^{2+} imaging from layer 2/3 excitatory neurons across the dorsal cortex, as mice perform the task. Our preliminary findings show that cortical activity patterns vary according to task epochs, consistent with distinct large-scale networks supporting different cognitive computations. Moreover, comparing activity levels between trials of long or short duration revealed that areas of the frontal cortex are preferentially engaged during longer-lasting computations, regardless of their identity, while the pattern of posterior recruitment is computation specific. Strikingly, the pattern of cortical recruitment during short-term memory could be largely explained by a hierarchy of spontaneous timescales, measured separately from the task. Taken together, our findings suggest that the identity and duration of a cognitive computation interact to determine large-scale cortical activity patterns during decision making.

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Poster

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Topic: H.05. Working Memory

Support: Simons Pilot Award: 872599SPI
NIH grant T32 AG020506

Title: Timescale-specific functional connectivity between layer 2/3 cortical neurons.

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Abstract: The cortex is organized into a macroscopic hierarchy of spontaneous timescales, which are shorter in sensory cortices than association areas. These timescales are likely fundamental to the computations performed by cortical regions, but the microcircuit mechanisms generating them are poorly understood. Specifically, they are likely influenced both by intrinsic neuronal properties, such as ion channel composition, and circuit properties like connectivity patterns. Here, we set out to understand how circuit properties give rise to distinct area-level timescales across cortical layer 2/3.

We first confirmed that the mouse dorsal cortex is organized into a timescale hierarchy. We performed mesoscale widefield Ca2+ imaging from head-fixed mice expressing GCaMP6s in excitatory layer 2/3 neurons (Cux2-Cre x Ai96 cross), while they ran in the dark. Mirroring previous findings in humans and macaques, we found a timescale gradient increasing from posterior sensory areas to frontal and medial association areas. To understand how circuit properties generate timescales, we performed cellular-resolution 2-photon Ca2+ imaging from mouse layer 2/3 pyramidal cells co-expressing the calcium sensor GCaMP6s (Thy1 promoter) and the red-shifted excitatory opsin ChRmine (CamKII promoter). We imaged from either the visual cortex (V1) or the premotor cortex (M2) during spontaneous running. We found broad distributions of neuronal timescales in both areas, but that V1 neurons have shorter timescales than those in M2. Additionally, neurons in M2 were spatially clustered according to their spontaneous timescales. To understand how connectivity patterns in different cortical areas give rise to their macroscopic timescales, we have been performing all-optical functional connectivity measurements, optogenetically stimulating single neurons while measuring network responses with two-photon microscopy. In M2, we found that stimulation of long-timescale neurons is more likely to evoke activity in the network. Neurons display timescale-specific functional connectivity: ensembles of short- or long-timescale neurons are preferentially connected with themselves. We are currently performing similar experiments in V1 to understand how cortical areas differ in their functional connectivity properties.

This work begins to elucidate how distinct cortical networks can create unique profiles of activity timescales, contributing to our mechanistic understanding of cortical computation. Our future work will focus on timescales in the context of behavior, to examine how these properties could underlie cognitive processes such as working memory and task selection.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Title: Novel analysis of cerebrocerebellar interaction based on spontaneous peaks in oscillation power detects defects in the cerebral cortical functional connectivity in Engrailed1/2 conditional knockout mice

Authors: *Y. LIU[1], M. FOX[2], B. C. CHAPMAN[3], A. S. LEE[4,5], A. L. JOYNER[4,5,6], D. H. HECK[1];
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Abstract: We simultaneously recorded local field potential activity in the cerebellar nuclei (CN) of control mice (CT) and *Atoh1*-conditional knockout mice (KO) with loss of the homeobox transcription factor genes Engrailed1/2 (*En1/2*) in embryonic excitatory cerebellar neurons, including all excitatory cerebellar nuclear neurons (eCN). Conditional loss of En1/2 in Atoh1-derived neurons results in preferential loss of eCN in the posterior domains of the medial and intermediate CN. These mutants allow us to investigate the role of these genes in eCN function and contribution of these neurons to various brain functions. Time resolved analysis of the power of neuronal oscillations in the CN shows spontaneous fluctuations in power that independently occur in different frequency bands. There is increasing evidence supporting a cerebellar role in coordinating communication between cerebral cortical areas through modulating the coherence of neuronal oscillations. Here we asked whether the occurrence of oscillation power peaks in the CN is associated with changes in the coherence of neuronal oscillations in the medial prefrontal cortex (mPFC) and dorsal hippocampal CA1 region (dCA1). We detected power peaks that exceeded 2 standard deviations of the baseline power fluctuations and marked the times of power peak onsets and ends as temporal aligns for further analysis. We marked power peaks in this way in each of the traditional frequency bands used for neuronal oscillations. Electrophysiological signals were captured with an eCube Server (White Matter LLC) and analyzed offline in Matlab (MathWorks, Inc.). Recordings were performed in 6 CT and 6 KO mice. We performed time resolved analysis of coherence between the mPFC and dCA1 aligned on the onset of power

peaks in the CN. In both CT and KO mice CN power peaks occurring in the high-gamma band (80-100 Hz) were found to be associated with significant increases in mPFC-dCA1 coherence across a broad frequency range (60-200 Hz). For both groups coherence values reached their maximum after power peak onset. In KO mice the mPFC-dCA1 coherence increase aligned on CN power peak onset reached significantly higher values than in CT mice, suggesting changes in cerebrocerebellar communication in the KO mice possibly due to the partial loss of eCN. These findings support the idea of a cerebellar involvement in the modulation of coherence between cerebral cortical areas and that coherence between the mPFC and dCA1 may specifically require an intact population of eCN in either the posterior medial or interposed nucleus or both.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Topic: H.05. Working Memory

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NIH National Institute of General Medical Sciences grant R01GM134363-01

Title: Neuronal timescales are dynamic and not intrinsic during human working memory

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Abstract: Cognition operates at timescales spanning several orders of magnitude: from millisecond auditory perception to lifelong goal planning. While a great deal remains unknown about how the brain represents these timescales, recent research suggests that neural populations have intrinsic timescales that are hierarchically organized across the cortex. In this view, neurons in lower sensorimotor regions have shorter timescales, encoding information briefly before activity returns to a relatively uncorrelated state. In contrast, neural timescales are longer in association cortices, where activity can be maintained for seconds or more. However, the scope of this research in empirical data in humans is often limited to resting-state contexts, which may result in neural timescales being interpreted as intrinsic, and not dynamic. There is a gap in the research linking neural timescales with cognitive tasks that require the manipulation of information over varying timespans.
Here, we investigate the possibility that neuronal timescales are not strictly intrinsic, but rather are dynamic and task-related modulated as a function of task demands. To analyze this, we leveraged an open-access dataset (taken from Johnson et al. (2018)) that includes intracranial electroencephalography (iEEG) recordings from patients performing a visual working memory

task. The task entailed experimental control of temporal processing of stimuli: whereas short-timespan conditions require simple stimulus feature-response mappings, longer-timespan conditions require responses contingent upon the temporal relationships of stimuli. We predicted that timescales will be longer for conditions requiring longer timespans of integration.
We first replicate previous findings that showed that, collapsing across all timespan conditions, neural timescales lengthen during a working memory delay period (as compared to a pre-trial baseline). We additionally find trending effects of condition-specific modulation of neural timescales, whereby task conditions demanding integration across longer timespans exhibit modestly longer neural timescales.
Given that the majority of neural timescales research is focused on "intrinsic" resting-state derived timescales, this work is a critical first step in establishing their functional relevance in human cognition.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Topic: H.05. Working Memory

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Title: Distinct neural codes of mnemonic and sensory representations in early visual cortex

Authors: *S. KIM[1], J. LEE[1], H. GU[2], M. CHOE[1], H. LEE[1], J. LIM[1], H.-J. LEE[1], D.-G. YOO[1], S.-H. LEE[1];
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Abstract: Many studies have shown that working memory (WM) representations can be found in the early visual cortex (EVC) (Harrison and Tong, 2009; Serences et al., 2009; Ester et al., 2013). The sensory recruitment hypothesis postulates that EVC uses the same code to represent WM as it does for sensory representations ('sensory code'), which allows WM to benefit from the high fidelity of the sensory code (Adam et al., 2022; D'Esposito and Postle, 2015). However, a recent study challenges this view, reporting that EVC's population activity pattern during sensory encoding does not match that during WM maintenance (Kwak and Curtis, 2022). Here, to examine whether EVC uses the same code to represent sensory and mnemonic information, we developed a paradigm where sensory and mnemonic representations are sufficiently separated in time and compared them using several measures of neural codes.

In an MRI scanner, human observers (N=50) briefly viewed an oriented grating and reproduced its orientation after a long delay period (16.5 s), which is long enough for the blood-oxygen-level-dependent (BOLD) responses to the grating to dissipate. The sensory representations were defined from the BOLD responses during the period when the univariate BOLD activity peaked. On the other hand, the mnemonic representations were defined from those during the last moment of the delay period.
The sensory and mnemonic representations differed in the following aspects. First, when projected onto a low-dimensional state space, the sensory and mnemonic orientations were formed in the two separated planes orthogonal to each other. Second, when the inverted encoding model (Brouwer and Heeger, 2009) was trained to decode stimulus orientation, the mnemonic orientation information could not be decoded using the voxel weight trained to the sensory representations, whereas the sensory orientation information could not be decoded using the voxel weight trained to the mnemonic representations. Third, when inspected for behavioral relevance, the errors in the reproduction task were better predicted by the orientations decoded in the mnemonic representation than those decoded in the sensory representation. Lastly, when examined for retinotopic properties, the voxels' orientation preferences in the sensory representation were tightly correlated with their radial positions in retinotopic space, whereas their preferences in the mnemonic representation did not display such a correlation.
Our findings suggest that EVC uses distinct codes to represent sensory and mnemonic orientations. This would allow the brain to carry out tasks that involve comparing both types of representations without interference.

Disclosures: **S. Kim:** None. **J. Lee:** None. **H. Gu:** None. **M. Choe:** None. **H. Lee:** None. **J. Lim:** None. **H. Lee:** None. **D. Yoo:** None. **S. Lee:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR301.07/VV13

Topic: H.05. Working Memory

Support: National Natural Science Foundation of China's Major Scientific Research Instrument Development Project 31827803

Title: Brain-wide neuronal activity underlying memory-to-decision transformation

Authors: *Y. WANG[1], C. T. LI[2];
[1]Inst. of Neuroscience, CAS, shanghai, China; [2]Inst. of Neurosci., Shanghai Inst. of Biol. Sciences, Chinese Acad. of Sci., Shanghai, China

Abstract: Brain-wide neuronal activity underlying memory-to-decision transformation**Abstract:** Cognitive processes are intertwined to mediate behavior. How neural substrates underlying these processes are globally organized to guide behavioral performance is unclear. Here we developed

a new behavioral paradigm consisting with two delay periods. In this task head-fixed mice need to maintain odor-memory information during the first delay period, comparing it with the test-odor information during the test-delivery period, and maintain the left or right-choice information during the second delay period. Successful performance of the task requires mice to use the working-memory information during the test-odor delivery period. Thus, population neural activity will be transformed from maintaining sensory information into maintaining choice information. We then used Neuropixels probes to simultaneously record brain-wide single-unit activity in mice performing the task. Optogenetic suppression was also performed in designed brain regions, including prefrontal cortex, mediodorsal thalamus, and anterior piriform cortex, which showed differential activity patterns as revealed by Neuropixels recordings. Our results shed important insights on brain-wide neural mechanisms underlying cognition, specifically in memory-to-decision transformation.

Disclosures: Y. wang: None. **C.T. Li:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR301.08/VV14

Topic: H.05. Working Memory

Support: ERC Grant 2021

Title: Interhemispheric Sensory Flow: Unraveling Sensory information and Working Memory transfer in Mouse Cortical Posterior Areas

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Abstract: The interhemispheric transfer of information in the cortex plays a significant role in the way we perceive the world. The cortex does not only integrate sensory information but is also required to retain information in memory for several seconds. This function is defined as working memory (WM) and is thought to be encoded across many brain areas. Whereas the process of sensory information and WM in one hemisphere has been broadly investigated in previous studies, interhemispheric transfer of sensory information and WM is poorly understood. We trained mice expressing calcium indicators across layer 2/3 of the cortex, to match between two textures (smooth or rough sandpapaers) from both sides of their whiskers in a go/no-go task. Matching textures required mice to lick for a reward (Hit), and non-matching textures required withholding licking (correct rejection; CR). Once the mouse has reached expert level, we introduced a delay period in-between textures presentation. Thus, the WM of the first stimulus needs to be retained and transferred to the other hemisphere. Using dual-hemisphere wide-field calcium imaging, we compared cortex-wide neuronal activity to study interhemispheric transfer of sensory information and WM. We found involvement of the Barrel cortex (BC) in processing

choice-information, where ‘Hit’ displayed higher activity compared to ‘CR’. Furthermore, BC did not encode the type of texture, as there was no discernible difference in BC activity between ‘Hit’-smooth and ‘Hit’-rough during the sensation epoch. By introducing a delay period (1-3 sec) between texture presentations, we observed sequential activity across hemispheres in posterior areas. Specifically, the left posterior area (P) initially held the sensory and type-information at the beginning of the delay period and subsequently transferred it to the homotopic P area even before the arrival of the second texture. Moreover, we found additional posterior areas such as the posterior-medial (VISpm) and the retrosplenial-dorsal (RD) involved in the transfer of WM. To further investigate the areas involved in choice and/or texture information during the WM transition, we used a support vector machine (SVM) to classify choice or texture type based on neuronal signals across the entire cortex. This analysis enabled us to outline which areas contribute to the mouse's decision based on the sensory input. Consequently, our dual hemisphere behavioral task and imaging approach provide valuable insights into the processing and availability of sensory information for daily activities.

Disclosures: **E. Avidan:** None. **S.D. Sherer:** None. **S. Yadlin:** None. **A. Gilad:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

Location: WCC Halls A-C

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Topic: H.05. Working Memory

Support: NRF of Korea, Basic Science Research Program (2020R1A2C2007770)
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Title: Dynamic changes in neural representations during selective long-term memory retrieval in the prefrontal and parietal cortex

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Abstract: Goal-dependent retrieval of selective information from long-term memory (LTM) is pivotal for guiding our behaviors. State-based models of working memory propose that the contents of working memory are representations from either perception or LTM that are in an activated state, controlled by attentional processes. However, the specific neural mechanisms underlying goal-dependent information processing during selective retrieval from LTM remain poorly understood. To address this gap, we conducted an event-related functional magnetic imaging (fMRI) experiment comprising distinct learning and retrieval sessions. During the learning session, participants memorized scenes in which multiple objects are naturally placed.

On the following day, the participants were asked to selectively retrieve a cued object from the memorized scenes while being scanned in the MRI, followed by separate scans of object and scene perception. By employing multi-voxel pattern analysis, we found representational dynamics over time in the dorsolateral prefrontal cortex (dlPFC) and angular gyrus (AG) during selective retrieval of long-term memory. The direct comparison of neural response patterns during selective retrieval with those elicited by perception revealed distinct patterns of representation in the AG and dlPFC. Specifically, during the early phase of retrieval, both the AG and dlPFC represented the retrieved scene information. However, the AG primarily represented the targeted object, while the dlPFC showed prominent representation of non-targeted objects. In the later phase of retrieval, shared representation between retrieval and perception was not observed in either area. Instead, there was a persistent retrieval cue-specific representation in both the dlPFC and AG throughout the later phase. Further analysis of pattern similarity between adjacent time points during retrieval confirmed a distinction in neural representations between the early and later phases of retrieval. These results suggest that selective long-term memory retrieval involves not only distinct information processes in the prefrontal and parietal cortex but also dynamic changes in information processing over time in these cortical areas.

Disclosures: J. Park: None. **S. Lee:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Topic: H.05. Working Memory

Support: NIH R01MH062349
Simons Foundation 543057SPI

Title: Connectome-constrained multi-area recurrent neural networks performing working memory tasks

Authors: *W. SOO[1], X.-J. WANG[2];
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Abstract: Over the past decade, recurrent neural networks (RNNs) have been widely adopted as mechanistic models of the brain. Fundamentally, they provide insights on how a group of interconnected neurons can function together as a single network to perform specific brain functions or cognitive laboratory tasks. However, due to memory constraints, RNNs trained in the past are small (ranging from 2 to 100 neurons). For the same reason, such networks typically model specific brain areas such as the prefrontal cortex, while oversimplifying the functionalities of other areas. In recent years, computational constraints have been greatly reduced due to

improved computing hardware. Yet, RNN models in neuroscience continue to adopt the same simplifying assumptions which undermines the expressivity of such models.
Here, we address these issues by training RNNs comprising of 15 distinct brain areas, including 2 early visual areas, 3 ventral visual areas, 4 dorsal visual areas, 2 areas corresponding to frontal eye fields and 4 prefrontal areas. The interareal synaptic weights between any two brain areas are constrained by experimentally-measured connectomic data. Visual stimulus is presented only to a single area, V1, resulting in a change in neural activity within V1 which then propagates to higher-order areas. The functionality of each brain area (such as identification of stimulus position by the dorsal visual areas) is incorporated by supervised learning. At the same time, the networks are trained to perform 1 of 9 visual working memory tasks. The responses of the networks are read out from the frontal eye fields, representing a saccadic response similar to subjects in laboratory settings. We find that our trained networks achieve their training objectives using well-understood attractor dynamics, where sensory areas employ stable population codes while prefrontal areas exhibit dynamic coding properties. We formulate a principled mathematical framework to quantify information transfer between areas. This allows us to understand how information is transferred between areas, as well as how information is held in working memory. With these results, we compute an information hierarchy across brain areas, which we find to closely match an experimentally-derived hierarchy. When the training is repeated without connectomic constraints, we find that the trained networks employ biologically-implausible degenerate solutions. Our results represents an improvement in the expressivity of trained RNNs in neuroscience, and our proposed framework of information flow represents a unique approach to understanding the mechanisms underlying these complex and intractable models.

Disclosures: **W. Soo:** None. **X. Wang:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

Location: WCC Halls A-C

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Program #/Poster #: PSTR301.11/Web Only

Topic: H.05. Working Memory

Support: UNAM DGAPA PAPIITIG300121
CONAHCYT960289

Title: Neurophysiological responses during the binding process in working memory

Authors: *J. MARCUÉ-ARANA, S. CANSINO;
Lab. of NeuroCognition, Univ. Nac Autónoma de México, Mexico City, Mexico., Mexico City, Mexico

Abstract: Working memory is a limited-capacity system responsible for handling and temporarily maintaining information. The multicomponent model of working memory includes

the episodic buffer, which encodes, retains, and integrates multimodal information from the visuospatial sketchpad and the phonological loop. Although the model is highly accepted, little research has been conducted to examine the binding process in working memory. This research aims to examine the neurophysiological similarities and differences of three different kinds of binding according to their modality: visual-visual, verbal-verbal, and visual-verbal. Event-related potentials were recorded in 30 participants while two pairs of stimuli from the different binding modalities were presented, followed by a single pair. Participants indicated whether the single pair was equal to one of the previous two pairs even if the stimulus position was changed, or was not equal to any of them. Subsequent correct unimodal binding, compared to that for multimodal binding, elicited during codification a greater P300 and sustained positive wave (SPW). The P300 was observed in frontal sites and central middle derivations, and the SPW was observed in frontal and central sites. During retrieval, a similar pattern was observed for these same components. However, for the P300, the effect was detected in the frontal, central, and occipital left sites. Different neurophysiological patterns characterize the binding of modalities compared to those associated with the binding of information from the same modality.

Disclosures: J. Marcué-Arana: None. **S. Cansino:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Topic: H.05. Working Memory

Support: NRF of Korea, Basic Science Research Program (2020R1A2C2007770)
NRF of Korea, Neurological Disorder Research Program (2020M3E5D9079913)
SNU, New Faculty Startup Fund

Title: Differential information processing in the parietal cortex during tactile-visual cross-modal transfer

Authors: *D. PARK[1], Y. RYOO[1], K. LEE[2], S. HWANG[2], H. F. KIM[2], S.-H. LEE[3];
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Abstract: Perceiving the spatial characteristics of objects, such as shape, occurs through both visual and tactile modalities in our daily lives. Moreover, object information obtained through visual perception can be transferred or predicted to the tactile modality, and vice versa. Previous research has suggested the involvement of the posterior parietal cortex in the integration and cross-modal transfer of tactile and visual information. However, the neural mechanism underlying the transfer of information for the same object between visual and tactile modalities remains unclear. To directly investigate the neural processing associated with visual-tactile

cross-modal transfer, we conducted neural response measurements using functional magnetic resonance imaging while participants performed delayed match-to-sample tasks. During these tasks, participants were instructed to retain a tactile or visual braille stimulus and determine whether the maintained information matched the test stimulus presented in the same or different sensory modality. The participants successfully retained tactile or visual information during the delay period in both within-modal tests (visual-to-visual or tactile-to-tactile) and cross-modal tests (tactile-to-visual or visual-to-tactile). Our findings reveal that superior parietal cortical regions, including superior parietal lobule and intraparietal sulcus, retain stimulus identity information during the delay period in both within-modal and cross-modal tests. Furthermore, cross decoding of individual stimuli between different within-modal tests, as well as the cross decoding between the cross-modal tests, was possible in the superior parietal cortex. However, such cross decoding was observed only during the cross-modal tests, not during the within-modal tests in the inferior parietal regions including the angular gyrus. These results suggest the existence of differential information processing in the superior and inferior parietal regions during the process of cross-modal transfer.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

Location: WCC Halls A-C

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Topic: H.05. Working Memory

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Walter F. Heiligenberg Professorship

Title: Effects of the Persistence of Theta Oscillations during Working Memory Retention on the Information Flow between Hippocampus and Medial Prefrontal Cortex

Authors: *Y. LI[1], L. TONG[1], F. FAROUQ[1], W. LI[1], J. LEUTGEB[1,2], S. LEUTGEB[1,2];
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Abstract: The hippocampus (HPC) and medial prefrontal cortex (mPFC) are essential for working memory (WM) maintenance, with both regions required for the dynamic process of holding information in memory for future decisions. Anatomical and functional connections between HPC and mPFC enable efficient communication between brain regions during WM tasks. Specifically, ventral HPC is directly connected to mPFC, which facilitates the transmission of neuronal firing patterns in one area to the other. Furthermore, there is evidence of oscillatory

coupling, with dorsal HPC leading theta-related prefrontal activity and ventral HPC leading gamma-related prefrontal activity. Despite these findings, it remains unclear how the direction of information flow between HPC and mPFC is controlled by oscillatory activity during different behavior phases, and in particular, during WM retention in the delay interval. To address this gap, large-scale neural recordings along the entire septotemporal axis of HPC and along dorsal to ventral regions of mPFC were performed with two chronically implanted Neuropixels probes in rats in a delayed spatial alternation task. The task included delay intervals of 10-s or 30-s and blocks of trials when rats were either forced to run on a treadmill or allowed to rest. The latter manipulation allowed for the examination of neuronal firing patterns during different brain states - with and without ongoing theta oscillations. As expected, theta power was significantly lower when rats were resting compared to running during the delay. Despite the differences in oscillation patterns, reliable time cells were limited to the first few seconds in both conditions and in 10-s as well as in 30-s delay intervals at recording locations along the entire septotemporal axis of HPC. In 30-s delay intervals, a second population of late-firing cells was observed, which was silent during the first few seconds, but then constitutively active across the remainder of the delay period. With WM lasting 30 s in our experiment and time cell sequences in all hippocampal regions only occurring during the initial few seconds of the delay, WM maintenance likely requires mechanisms other than the sequential activity of hippocampal time cells. We are therefore now testing to what extent mPFC neuronal activity patterns might support WM in delay intervals when different oscillation patterns predominant. By elucidating the directionality of information flow between these regions during different brain states during the retention interval, we anticipate that our findings will contribute to a more complete understanding of the functional dynamics between HPC and mPFC that support WM.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Title: Theta-associated high-frequency oscillations in the CA3-DG network predict future choices in a dentate-dependent working memory task

Authors: *M. WANG[1], Y. ZHANG[1], T. SASAKI[3,4], S. LEUTGEB[1,2], J. LEUTGEB[1,2];
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Abstract: Different brain states associated with behavior are characterized by a wide range of oscillatory frequencies that reflect distinct underlying network mechanisms to support different phases of memory. Yet, memory-guided behavior requires the uninterrupted retention and updating of task-relevant information across numerous transitions between brain states. One of the remaining key outstanding questions is thus how information is not only retained but also organized to become task-relevant throughout these transitions. To study this question, we will focus on the hippocampal dentate-CA3 network where we have recently shown that the dentate gyrus (DG) is critical for the generation of prospective coding of future correct choices by CA3 cells during sharp-wave ripples (Sasaki et al., *Nat Neurosci,* 2018) in a dentate-dependent working memory (WM) task. While our previous work determined that prospective coding occurred during SWRs at reward locations for possible correct choices, here we analyze activity during theta oscillations within intervening periods. Dorsal DG-CA3 ensembles were assessed while male Long-Evans rats performed a spatial memory task on the eight-arm radial maze. In this task, reward consumption at each of the eight locations requires updating of memory about the remaining goal locations. We identified prominent high frequency (150-250 Hz) local field potential (hf-LFP) events in CA3 during active exploration between reward sites. The CA3 hf-LFP events were associated with increased CA3 population activity at the trough of theta, and correlated with increased DG neural activity, but not with high-frequency LFP in CA1. Bayesian decoding of CA3 neural activity during CA3 hf-LFP events reliably predicted the next upcoming choice of animals at choice points. The same correlation was not observed during periods when WM was not needed, suggesting a role of hf-LFP in WM-guided decision-making. Compared with sharp-wave ripples at reward, the CA3 hf-LFP events during movement displayed lower neural firing synchrony but were associated with higher DG neural activity. Taken together, in an effort to explore how network mechanisms across different brain states support WM, we observed neural activity that supports the hypothesis that the neuronal representations of all available choices are played out during SWRs, while a selection of the next choice can be predicted during the subsequent theta state.

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Poster

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Topic: H.05. Working Memory

Support: NIH R01 EY-016407
R01 EY-033925 (CEC)

Title: Visual working memories are abstractions of percepts

Authors: *Z. DUAN, C. E. CURTIS;
New York Univ., New York City, NY

Abstract: Following pioneering studies demonstrating that patterns of multivoxel activity in early visual cortex can be used to decode the contents of visual WM (Harrison and Tong, 2009; Serences et al., 2009), decoding from visual cortex has been a workhorse for neuroimaging studies testing aspects of the sensory recruitment hypothesis of WM. This hypothesis posits that visual WM storage utilizes the encoding machinery in visual cortex, often assuming that memory and perception rely on similar mechanisms. Although a vast majority of this work has used oriented gratings as memoranda, the interpretation of a number of fMRI decoding studies involving the perception of oriented gratings has been challenged. Rather than simply a reflection of orientation tuning, orientation decoding depends on complex interactions between the orientation of the grating, the aperture edges, and the topographic structure of the visual map (Carlson, 2014; Roth et al., 2018). Here, our goal is to both 1) test how these aperture biases described during perception may affect WM decoding, and 2) leverage carefully manipulated visual stimulus properties of gratings to disambiguate sensory-like WM codes from recoded abstractions of sensory features. We used as memoranda gratings multiplied by radial and angular modulators to generate orthogonal aperture biases despite having the same orientation. Therefore, if WM representations are simply maintained sensory representations, they would be predicted to have similar aperture biases. If they are abstractions of sensory features, they would not be biased and the modulator would have no effect on orientation decoding. Results indicate that patterns of delay period activity while maintaining the orientation of a grating with one modulator (eg, radial) are interchangeable with patterns while maintaining a grating with the other modulator (eg, angular). We find significant cross-classification in early visual and parietal cortex suggesting that WM representations are insensitive to aperture biases during perception. During a perceptual control task without memory, we demonstrate the aperture bias and find a lack of cross modulator decoding in these areas. Finally, we visualize memory abstractions of stimuli using a population receptive field model of the visual field maps (Kwak & Curtis, 2022). Regardless of the modulator and sinusoidal nature of the carrier grating, the WM representation takes on the appearance of a single oriented line. These results provide strong evidence that visual WM representations are abstractions of percepts, immune to perceptual aperture biases, that form efficient codes proximal to behavioral demands.

Disclosures: Z. Duan: None. **C.E. Curtis:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Topic: H.05. Working Memory

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Vision Training Grant to SLM
NIH R01 EY-016407 to CEC
R01 EY-033925 to CEC

Title: Frontal persistent activity impacts the quality of working memory representations in early visual cortex

Authors: S. LI[1,3], ***S. L. MASTER**[2], K. K. SREENIVASAN[4], C. E. CURTIS[2];
[2]Psychology, [1]New York Univ., New York, NY; [3]Psychology, [4]Div. of Sci. and Mathematics, New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates

Abstract: One key prediction of the sensory recruitment hypothesis of working memory (WM) is that WM involves a coordination between visual cortex, where sensory features are stored, and frontal cortex, where top-down feedback signals to sensory cortex originate. Previous fMRI studies generally report robust persistent activity during memory delays in frontal, but not visual cortex, and precise decoding of WM content in visual, but not frontal cortex. Here, we test the hypothesis that persistent activity in frontal cortex may be the source of top-down signals that improve the quality of WM representations in visual cortex. To do so, we measured fMRI responses while human participants maintained a target location in WM over a long delay period, and then judged whether a probe was clockwise or counter-clockwise to the memoranda. Trials began with a cue as to whether the trial would be hard (probe very close to target) or easy (probe far from target) as a means to vary the effort, and presumably top-down input, needed. Delay activity in frontal cortex persisted above baseline and was greater for hard compared to easy trials. The accuracy and uncertainty of WM representations encoded in the population activity within early visual cortex, as measured using a Bayesian decoder, were also affected by task difficulty. Critically, in support of our hypothesis, we found that trial-by-trial variations in the amplitude of delay period activity in frontal cortex predicted the decoded accuracy and uncertainty in early visual cortex. Correlations were more robust when top-down signals related to effort were employed in the hard compared to easy trials. These results suggest that persistent activity in frontal cortex may in part reflect feedback signals targeting WM representations in visual cortex. We hypothesize that these feedback signals may sculpt population activity in visual cortex, improving mnemonic fidelity and reducing mnemonic uncertainty.

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Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Program #/Poster #: PSTR301.17/VV22

Topic: H.05. Working Memory

Support: NIH R01 EY-016407
R01 EY-033925 (CEC)

Title: Do perturbations to primary visual cortex impact visual working memory?

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[1]Dept. of Psychology, [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Despite 50 years of focus on the role of the prefrontal cortex in WM, neuroimaging studies in the past decade have repeatedly demonstrated that early visual cortex plays an important role in WM. For instance, precise information about the contents of WM can be decoded from V1. Such evidence led to the development of a sensory recruitment hypothesis of WM, which posits that visual WM storage utilizes the encoding machinery and mechanisms of visual cortex. However, a critical test of this hypothesis involves the degree to which early visual processing is necessary for accurate WM representations. To test this hypothesis, we used transcranial magnetic stimulation (TMS) to perturb neural activity in V1 in humans performing carefully controlled visual WM experiments. Participants maintained in WM stimuli that were either in or away from a portion of the visual field within which TMS to V1 evoked phosphenes. After a delay, they made memory-guided saccades towards a target (prosaccade) or to a mirrored location away from a target (antisaccade). This allowed us to test hypotheses about the potential role of V1 in simply maintaining a previous visual target, as well as potential roles in maintaining WM representations that were never retinally stimulated. Our preliminary results suggest that TMS to V1 produces no impact on visual WM in any of these conditions, despite that previous studies demonstrated that memory-guided saccade accuracy is highly sensitive to even very small perturbations, and despite that slightly stronger TMS evoked robust and spatially specific phosphenes. To mitigate interpretational issues with null effects, we simultaneously recorded electroencephalography (EEG) to assess the impact of TMS to V1 on a well established marker of WM maintenance. On control trials without TMS, we noted robust and sustained alpha (8-12 Hz) power lateralization with respect to the WM targets. TMS to V1 abolished the alpha lateralization confirming the effectiveness of our TMS procedures. However, after a few hundred milliseconds the typical alpha power lateralization reformed prior to the end of the delay period. Together, these preliminary results suggest that V1 activity may not be necessary for accurate visual WM under these specific conditions. On one hand, perhaps other types of stimuli, oriented gratings or dot motion, may depend more on V1 than simple target locations. On the other hand, a strong interpretation of these results might suggest that top-down signals from higher order cortex may re-write over errors or loss of information encoded in V1 during memory. In either case, our results indicate the sensory recruitment hypothesis of WM may need revision.

Disclosures: M. Dake: None. **C. Curtis:** None.

Poster

PSTR301. Distributed Mechanisms of Working Memory and Decision-Making II

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Program #/Poster #: PSTR301.18/VV23

Topic: H.08. Learning and Memory

Support: CSTC Grant 14071/100/d

Title: Comparative roles of prefrontal cortex and substantia nigra reticulata in value-based object search

Authors: M. ABBASZADEH[1], ***A. NARMASHIRI**[2,3], A. GHAZIZADEH[1,3];
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Abstract: Comparative roles of prefrontal cortex and substantia nigra reticulata in value-based object search
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Abstract: Recent evidence suggests that searching for valuable objects can become quite efficient (diminished dependance of search time on display size) given sufficient object-reward association. Both ventrolateral prefrontal cortex (vlPFC) and basal ganglia output, substantia nigra reticulata (SNr) are known to control gaze by projections to superior colliculus (SC) and encode object value memories. Here we report and compare single-unit activity in vlPFC and SNr in two macaque monkeys while they engaged in value-based search for a high-value object among low-value objects in target-present (TP) or target-absent (TA) trials. Both regions showed a stronger differentiation of TP and TA trials (value signal) in efficient search based on population average firing rate and on high gamma power (100-200 Hz) local field potential (LFP). The strength of firing and LFP value signal was correlated with search efficiency in both regions ($p<0.001$). Notably while the the onset of firing rate value signal in vlPFC and SNr was not significantly different ($p>0.05$) the onset of gamma value signal in vlPFC was significantly faster than SNr ($p<0.001$). Furthermore, vlPFC firing had a saccadic component that differentiated TP and TA trials in efficient search. SNr firing had a lower spatial selectivity for the location of target compared to vlPFC. Together these results suggest that while SNr firing rate suppression in TP trials disinhibits SC, it is vlPFC that provides the spatial information and the saccadic command to direct gaze toward valuable objects in search.**Keywords:** value memory, visual search, search efficiency, single-unit recording, prefrontal cortex, basal ganglia, substantia nigra reticulata, macaque monkey, LFP, spiking variability.

Disclosures: **M. Abbaszadeh:** A. Employment/Salary (full or part-time):; School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran. **A. Narmashiri:** A. Employment/Salary (full or part-time):; School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran. **A. Ghazizadeh:** A. Employment/Salary (full or part-time):; Institute for Research in Fundamental Sciences.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

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Title: Mechanisms for Learning Task State Representations in the Frontal Cortex

Authors: *P. NILCHIAN[1,2], M. EL-GABY[1], D. DUPRET[1], T. BEHRENS[1];
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Abstract: The tasks we encounter often share common structures. Therefore, forming generalized task structure representations may allow animals to re-use knowledge across tasks, thus solving new problems more quickly. However, how individual neurons represent task structures remains an open question. We previously developed an ABCD-structured task in which mice collected four water rewards (a-d) in a repeating sequence of four locations. As such, the animals continuously transitioned between four task states (A-D). We identified "state cells" in the medial frontal cortex (mFC). These neurons were tuned to particular task states. In this study, we investigated how state cells form during early learning. We used electrophysiological recordings from the mouse mFC, taken during tasks one and two; the first time animals experienced a task change. To identify newly formed state cells, we extracted neurons' putative preferred states and evaluated if the extent of state tuning changed between the tasks. We demonstrated that newly formed state cells display elevated tuning to spatial locations (i). However, we did not find evidence to suggest that state cells show increased tuning to auditory cues (ii) or water rewards (iii). Furthermore, we observed that neurons' state preferences changed between tasks. We demonstrated that such changes are random in task space. Our findings were consistent with a model in which newly formed state cells initially tune to spatial positions (i). Our study is one of the first to investigate how individual neurons represent task structures. This opens a window into understanding the computational principles underlying the formation of task structure representations at the cellular level.

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Poster

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Support: NSERC Discovery Grant
Canada Foundation for Innovation JELF
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Title: Individual differences in ventrolateral prefrontal cortex thickness and memory performance in adolescents and adults

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Abstract: Previous work has demonstrated a relationship between individual differences in brain structure and memory performance. One particular region that has been implicated in memory-related cognitive operations is the ventrolateral prefrontal cortex (vlPFC), which is involved in selecting between related memories. As adolescents still show differences from adults in retrieval success at this age, especially when tasks are challenging, these faculties of the vlPFC are likely still developing. Furthermore, past evidence suggests that the vlPFC is late to mature, and undergoes significant development throughout adolescence. However, the specific association between vlPFC structure and the ability to select among competing memories remains poorly understood. This study aimed to investigate how individual differences in vlPFC structure relate to memory performance. Adolescents (12-13 years old) and young adults (25-35 years old) first learned pairs of items with overlapping elements, which created memory competition. After, participants completed a retrieval task that assessed their ability to select the correct memory from among related ones. We used structural magnetic resonance imaging (MRI) processed with Freesurfer to quantify cortical thickness in regions of the vlPFC for each participant, and then examined the relationship between these measurements and performance on the retrieval task. Behaviourally, adults performed better on the retrieval task than adolescents, consistent with the notion that adolescents are still refining their ability to retrieve overlapping memories. Consistent with prior work, we also found that adults had a significantly thinner vlPFC than adolescents. Among adults, thinner vlPFC was associated with better memory performance, particularly in terms of response times. This relationship does not seem to be a general relationship between overall cortical maturity and memory performance, as we did not see the same associations when we considered the postcentral gyrus as a control region. Additionally, the association was not observed broadly across all cognitive tasks, as vlPFC thickness was unrelated to performance on a separate attentional control task. Further analyses will investigate whether individual differences in vlPFC structure are related to age, self-reported pubertal maturity, and anxiety/depression scores. These findings offer novel insights into the neurobiological underpinnings of memory selection during adolescence, emphasizing the role of individual differences. Variations in the structural maturity of this region may contribute to individual differences in memory abilities.

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Poster

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Support: Wellcome trust grant 206401/Z/17/Z
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Title: Defining the cellular and circuit contributions of medial prefrontal cortex interneurons in associative recognition memory

Authors: *G. YVON-DUROCHER, P. J. BANKS, G. R. I. BARKER, C. BOOTH, E. C. WARBURTON, Z. I. BASHIR;
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Abstract: Associative recognition memory, such as recognising your misplaced house key or finding your car in a carpark, requires the quick integration of familiarity, spatial location and temporal information that is vital for everyday learning and episodic experience. The medial prefrontal cortex (mPFC) is a key integration hub within the associative recognition memory circuit as it receives long range excitatory inputs from the nucleus reuniens (NRe) and intermediate hippocampus (iCA1), both pathways being critical for learning. It is well known that inhibitory interneurons play essential roles in spatial and working memory function by gating signal flow and sculpting microcircuit dynamics. However, there is little understanding of the role mPFC interneurons have in associative recognition memory and its networks. Combining intersectional transsynaptic viral tracing, slice electrophysiology and *in vivo* wireless optogenetics, this project investigates; 1) if parvalbumin (PV), somatostatin (SST) and neuron derived neurotrophic factor (NDNF) interneurons in mPFC are involved in different phases of associative recognition memory, 2) the anatomical distribution and possible convergence of afferent excitatory projections from the iCA1 and NRe onto mPFC interneurons and 3) if these projections differentially engage interneuron subtypes, to bring about discrete modulation of mPFC network activity.
Using PV, NDNF or SST^{Cre} female and male mice (>8 weeks old), we show that iCA1 and NRe projections have distinct laminar distribution within the prelimbic cortex, NRe predominately targets layer 1 (L1) whereas iCA1 inputs are more uniformly distributed across prelimbic layers. Interneuron expression patterns showed spatial segregation, SST within layers 2-5, PV in 5/6 and NDNF interneurons predominately within L1. However, we also found NDNF positive cells within the dorsal tenia tecta that were GAD65/67 negative. Optogenetically activating iCA1 and NRe inputs differentially recruited PV interneurons compared to pyramidal neurons and had opposing short term plasticity at L1 NDNF interneurons. Wireless, in vivo optogenetic inhibition of NDNF and PV interneurons during an object in place associative recognition task is currently being undertaken and results analysed, with preliminary results showing high specificity of the inhibitory opsin. This work reveals that mPFC interneurons not only receive iCA1 and NRe inputs, but also differentially integrate these signals into mPFC microcircuits that could ultimately modulate distinct phases of associative recognition memory.

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Poster

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Topic: H.08. Learning and Memory

Support: ANR Grant EURE0028

Title: Distinct neuronal populations differentially contribute to prefrontal encoding of threat-related information

Authors: *A. MENEGOLLA[1], G. LOPEZ-FERNANDEZ[2], C. HERRY[2], M. MARTIN-FERNANDEZ[2];
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Abstract: In face of a threat, animals must choose one among a range of defensive behaviors, and the selection of a response suitable to each situation is essential for their survival. This response selection relies on the characteristics of the threat itself and its multimodal integration with environmental features that constrain the repertoire of strategies used to cope with the threatening encounter. With a novel paradigm that allows the execution of different defensive behaviors in response to distinct threatening situations, we recently demonstrated that neuronal populations in the dorsomedial prefrontal cortex (dmPFC) encode both a general danger state and specific threats. However, how these general and specific threat representations arise from the coordinated activity of different neuronal populations and guide the selection of the most adaptive defensive response in each threatening condition remains to be elucidated. To investigate this, calcium imaging on pyramidal ($CaMKII^+$), parvalbumin- (PV^+) and somatostatin-expressing (SST^+) neurons of the dmFPC was performed while mice executed the novel behavioral paradigm. Although the presence of a threat could be predicted from the patterns of population activity of all neuronal types, we observed a higher SST^+ unspecific activation compared to other neurons. Indeed, threat-related information was found to be more robustly encoded by the SST^+ population than by the PV^+ and $CaMKII^+$ ones. Furthermore, SST^+ neurons were the only neurons generating a sustained representation of safety during the discrimination of neutral from threatening stimuli. With this work, we started to identify how threat-related information is encoded in distinct prefrontal neuronal populations and how their coordinated activity gives rise to population representations of threats and contributes to the selection of defensive behaviors.

Disclosures: **A. Menegolla:** None. **G. Lopez-Fernandez:** None. **C. Herry:** None. **M. Martin-Fernandez:** None.

Poster

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The Uehara Memorial Foundation
The Naito Foundation

Title: A subpopulation of locus coeruleus noradrenergic neurons projecting to prefrontal cortex regulate flexible memory processes during contingency reversal

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Abstract: In changing environments, adaptive decision making requires memory processes that allow flexible reference and updating memory. Locus coeruleus noradrenergic neurons (LC-NA) are involved in controlling memory processes in accordance with current task demands, however the underlying neural circuit mechanisms are still unclear. Previous studies have reported that the prefrontal cortex (mPFC) and hippocampus, both of which receive LC-NA innervation, are involved in flexibility and learning, suggesting these connections may be key. Here, we examined LC-NA circuits involved in reversal learning which requires flexible memory processes. First, we examined the anatomical organization of LC-NA projections to the mPFC and the hippocampal CA1 region by using retrograde tracing with adeno-associated virus vectors (retroAAV). We injected retroAAVs carrying constructs that encode different fluorescent proteins (EYFP and mCherry) into the mPFC and the CA1 and found that a small number of LC-NA overlapped, with distinct populations of LC-NA projecting to the mPFC and the CA1 respectively. Next, we examined the involvement of mPFC-projecting LC-NA in reversal learning in a T-maze with chemogenetic inhibition of activity of mPFC-projecting LC-NA. Inhibitory Gi DREADD (designer receptor exclusively activated by designer drug) receptors were expressed in mPFC-projecting LC-NA. Subject mice were trained on the T-maze with one arm baited with a pellet and the other having no rewarded for three consecutive days, then the reward contingency was reversed and mice ran the reversal condition for four consecutive days. During the contingency reversal mPFC-projecting LC-NA were inhibited by injection of the DREADD ligand deschloroclozapine (DCZ), resulting in impaired reversal learning and suppressed head orienting behavior (“vicarious trial-and-error” (VTE)), which reflect memory-based deliberation after contingency reversal, at the choice point Our data suggest that the subpopulation of LC-NA projecting mPFC plays a role in flexible memory processes and adaptive decision making.

Disclosures: S. Amemiya: None. **T.J. McHugh:** None.

Poster

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Topic: H.08. Learning and Memory

Support: DFG JA 1999/3-1 ERC StG MEMCIRCUIT 758032

Title: Circuit mechanisms of dopamine teaching signals in mouse frontal cortex

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Abstract: As a neurotransmitter with extensive neuromodulatory properties, dopamine plays an important role in a wide range of distinct brain functions. A large body of experimental and theoretical evidence has shown that midbrain dopamine neurons are required for high-level cognitive processes generated by the medial prefrontal cortex (mPFC). Phasic dopamine transients encode a reward prediction error (RPE), which represents the difference between predicted and actual reinforcing outcomes. The RPE is a canonical learning signal, and converging evidence suggests that the mPFC functions as a crucial recipient for dopamine neuromodulatory signals to guide learning. However, the prefrontal neuronal mechanisms that govern this process are not known. We examined the role of dopaminergic transients in mPFC during abstract associative learning. Specifically, we investigated whether and how dopaminergic signatures evolve as task competency increases. We developed an auditory decision-making task with implicit (uncued) rules switches that was designed to capitalize on the hypothesized role of mPFC dopaminergic neuromodulation in cognitive processing and decision-making. Head-fixed mice learned to associate auditory cues with directed motor outputs (licks) to obtain liquid rewards. Auditory stimuli varied along the dimensions of location (left or right) and frequency (high or low). Only one feature dimension was relevant at a given time, depending on the currently applied task rule, which was changed after the animals reached expert performance levels. Dopamine concentrations in cortical areas are orders of magnitude lower than in the typically studied striatum, posing considerable experimental challenges for the investigation of prefrontal dopaminergic neurotransmission. To this end, we virally expressed the newly developed high-sensitivity fluorescent dopamine sensor GRAB DA3h in mPFC. Dopaminergic transients were measured with fiber photometry over the course of several months while the animals learned and re-learned the required tasks. Our efforts have resulted in successful dopamine recordings in the mouse mPFC with high levels of specificity and sub-second temporal resolution. Preliminary results show that the measured dopamine signals were event-locked and followed the task structure. Phasic dopamine transients evoked by the auditory cue and the obtained rewards were also modulated by the animals' performance levels and thus reflected their mechanistic understanding of the task. Together, our results will contribute detailed insights into the role of prefrontal dopaminergic neuromodulation in abstract associative learning.

Disclosures: **B. Righetti:** None. **T. Bernklau:** None. **S.N. Jacob:** None.

Poster

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Location: WCC Halls A-C

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Program #/Poster #: PSTR302.07/VV29

Topic: H.08. Learning and Memory

Title: Assessing Differences in Effective Network Connectivity during Reward-Based Learning in Children with Prenatal Drug Exposure

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Abstract: Prenatal drug exposure is prevalent worldwide, with 10% of pregnant persons using alcohol and up to 30% using tobacco. Prenatal alcohol and tobacco exposure in youth have been associated with higher impulsivity and worse reward-based learning, with previous literature demonstrating changes in microstructural neurodevelopment. There is little understanding of connectivity differences between these groups during reward-based learning. This study will leverage the Monetary Incentive Delay (MID) fMRI data from the Adolescent Cognitive Brain Development (ABCD) Study. The ABCD baseline cohort was stratified into four groups: prenatal alcohol exposure only (n = 895), prenatal tobacco exposure only (n = 225), prenatal alcohol and tobacco exposure (n = 174), and no exposure (n = 3049Based on prior meta-analyses, we chose six regions of interest that have been implicated in reward anticipation and reward outcome. Our stimuli of interest for hypothesizing effective connectivity models were reward anticipation and reward delivery. Results from a representative subject from each group show that anticipation of reward most suppresses the self-connection in the right frontal operculum in participants exposed to tobacco prenatally. For non-exposed individuals, anticipation of reward most suppresses the influence of the right frontal operculum on the right insular cortex. The goal is to understand the initial effective connectivity reward-learning state in 9-10-year-old youth and will be a step to further longitudinal analyses to track neurodevelopment of these connectivity patterns. In addition, with deficits in reward-based learning implicated as risk factors for substance abuse, we are interested in effective connectivity neurobiological risk factors for substance abuse and other psychopathologies associated with prenatal alcohol/tobacco exposure.

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Poster

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Program #/Poster #: PSTR302.08/VV30

Topic: H.08. Learning and Memory

Support: NRSA F32MH127878
R01 - MH126971

Title: Sequence generalization via modular curriculum learning

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Abstract: Many organisms use old skills and knowledge in new situations, as doing so strongly supports adaptive behavior. How humans and other primates accomplish this has been difficult to determine, but building general computations out of more basic capacities - i.e., compositional generalization - appears especially important. Simple sequence-based tasks often naturally require the latter, and we present work examining how recurrent neural networks solve them. To investigate this, we decomposed a sequence-learning task involving two forms of generalization into various plausible sub-tasks, and trained neural networks on combinations of these. Using restrictions on network training parameters and structure, we also enforced modularity, such that different sub-networks learned about different sub-tasks in some of our models. We hypothesize that networks differing in modularity and training curricula should show characteristic differences in learning speed, generalization, and error distributions, mediated by competence in relevant task primitives. These measures characterize the behavioral, performance characteristics of our networks, but we further expect that, mechanistically, unstructured networks should be less likely to learn the same sorts of representations as their modular, curriculum-trained counterparts as task complexity increases. Moreover, we expect that the extent to which unstructured networks generalized properly should correlate with their discovery of mechanisms similar to those employed by the modular, curricular networks. The specific sub-tasks we have trained networks on require tracking sequence-position, storing items in working memory, enumerating seen items, and predicting upcoming inputs based on observed associations. Preliminarily, we have observed that by training individual working memory networks, then training networks with multiple such sub-networks, our training success rate on the tasks for the larger networks are somewhat higher, as would be expected. We expect similar results to hold as we engage more curricula, and we plan to compare the mechanisms our models use to solve these tasks as outlined above. In addition to testing our mechanistic and behavioral hypotheses, our modeling experiments will be of broader relevance to psychiatric and aging neuroscientists. By exploring how compound behaviors and functional competence on task components are related, they will provide mechanistic hypotheses about the capacities of different cognitive systems to compensate for one another when important component functions, such as working memory, are impaired.

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Poster

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Topic: H.08. Learning and Memory

Title: Prefrontal glutamatergiic neurons present diminishing activity trhoughout a learning based task.

Authors: *E. S. NICOLAU[1], H. T. FERRER[1], L. V. MAGNO[2], A. NOGUEIRA[1], D. M. DE MIRANDA[1], M. ROMANO SILVA[1];
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Abstract: The medial prefrontal cortex (mPFC) plays a critical role in cognitive tasks; however, understanding the modulation of specific neuronal subtypes during these tasks remains an ongoing investigation. In this study, we employed fiberphotometry (FIP) to record the activation patterns of mPFC GABAergic and glutamatergic neurons in mice while they performed the BarnesMaze (BM) cognitive task over a 4-day behavioral trial. To enable simultaneous FIP and BM, we implemented a modified structural and procedural protocol for the BM, which was successfully validated. Our preliminary results demonstrate significant changes in the activation intensity and event frequency of both glutamatergic and GABAergic neurons in specific task contexts across the trial days. Moreover, when analyzed in relation to BM performance parameters such as task completion latency and adopted strategy, both glutamatergic and GABAergic neurons exhibited a significant decline in activation patterns and event frequency throughout the trial. These findings suggest that glutamatergic and GABAergic mPFC neurons play important roles in learning, memory, and decision-making, and that the activation patterns of these neuronal groups may serve as markers for cognitive progression and/or dysfunction.

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Poster

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Topic: H.08. Learning and Memory

Support: The McKnight Brain Research Foundation, NIH RF1AG067429

Title: Effects of chronic vagus nerve stimulation on cognitive performance in aging

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Abstract: Disruptions in both excitatory and inhibitory signaling within the prefrontal cortex (PFC) contribute to age-related impairments in executive functions. Moreover, these disturbances in neuronal excitability associated with age-related cognitive decline may interact with or worsen due to elevated inflammatory signaling, which is itself associated with cognitive impairments in aging. Electrical vagus nerve stimulation (VNS) is an approved treatment for intractable epilepsy and certain neuropsychiatric disorders, and some individuals receiving VNS therapy have reported improvements in cognitive function as a side effect. This current study has two aims: 1) to investigate the effects of chronic VNS on working memory in aging and 2) to investigate the effects of chronic VNS on inflammatory markers that are elevated with age and linked to cognitive dysfunction. Male and female FBN rats (24 mo.) were surgically implanted with a cuff electrode around the left vagus nerve. For aim 1, the rats underwent daily testing on a delayed response working memory task in operant chambers, in which they had to learn and remember the left/right position of a response lever over short delays. Rats were tested on the task in the mornings and received sessions of VNS in the afternoons using parameters shown previously to enhance cortical plasticity and other forms of PFC-dependent learning (100 stimulus trains/session at 30Hz, 700 µA, 120 µs biphasic pulse width, 0.8 s train duration). For aim 2, rats underwent the same VNS parameters for 30 days, and blood and brain samples were collected at the endpoint and analyzed using ELISA. Control groups for both aims consisted of rats implanted with sham cuffs that underwent identical procedures in the absence of VNS. Data to date show that after 25 sessions, rats that received VNS exhibited improved working memory compared to controls. In addition, after 30 days of VNS there was a significant reduction in circulating levels of galectin-3 (a lectin that can regulate and amplify inflammatory cell behavior, and that is elevated in aged compared to young adult rats) in comparison to controls. These findings suggest that chronic VNS has the potential to remediate age-related impairments in working memory, possibly via reductions in elevated inflammatory signaling that occurs in aging.

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Poster

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Program #/Poster #: PSTR302.11/VV33

Topic: H.08. Learning and Memory

Title: Prefrontal cortex simultaneously encodes interactive adaptive processes with slow and fast dynamics in value learning

Authors: *S. HASHEMIRAD[1], M. ABBASZADEH[2], A. GHAZIZADEH[3];
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Abstract: Prefrontal cortex simultaneously encodes interactive adaptive processes with slow and fast dynamics in value learning
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Abstract: Valuable objects such as food items, mates and currencies tend to keep their worth over time but every so often values of certain objects can change requiring flexible learning and memory. Previous work suggested a segregated network for stable and flexible value processes in the caudate nucleus tail and head, respectively; however, the neural circuitry underlying the interaction of these two processes remains unknown. Given the role of primate ventrolateral prefrontal cortex (vlPFC) in value learning and its broad connectivity with caudate nucleus, we recorded single-unit activity in two macaque monkeys (Monkey_H n=60, Monkey_P n=65) who performed a paradigm in which stable object values underwent an abrupt reversal using an object reward learning task. Free-viewing and passive-viewing tasks were used to probe changes in gaze bias and neural firing, respectively, before, immediately after, 15 minutes after and a day after the reversal training. The free-viewing results revealed a gaze bias switch immediately after reversal training. Notably, this switch faded after >15 minutes testing and reverted back toward the initial stable bias a day after the reversal training. We show that this snap-back phenomenon cannot not be produced by a single learning and forgetting rate but implies a value learning system with two processes one with fast learning and forgetting and the other with slow learning and forgetting. Interestingly, vlPFC neurons firing encoded both the slow and fast processes multiplexed in early and late component of their firing rates after object onset, respectively. The early part of firing consistently signaled the old object values and remained relatively unchanged following value reversal. On the other hand, the late component showed a change immediately after reversal which faded in the later testings. Taken together, these results suggest two interactive processes with slow and fast dynamics underlying value learning and memory and implicate vlPFC as the plexus for interaction of these two processes that possibly originate from caudate head and tail.
Keywords: prefrontal cortex, value reversal, slow and fast dynamics, single-unit recording, macaque monkey

Disclosures: **S. hashemirad:** A. Employment/Salary (full or part-time):; School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran. **M. Abbaszadeh:** A. Employment/Salary (full or part-time):; School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran. **A. Ghazizadeh:** A. Employment/Salary (full or part-time):; School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.12/VV34

Topic: H.08. Learning and Memory

Support: 20012355

Title: Reorganization of Prefrontal Cortical Neuronal Network during Conditional Fear Memory Consolidation

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Abstract: The prefrontal cortex (PFC) plays a crucial role in the consolidation of long-term memory (LTM) by interacting with the hippocampus and amygdala. While previous studies have explored the inter-regional connectivity between the PFC and these regions during fear conditioning, little is known about the changes in intra-regional networks within the PFC during memory consolidation. In this study, we investigated the network organization of the PFC neurons in rodents using the contextual fear conditioning paradigm. Mice were habituated to the experimental context and subjected to a conditioning phase with multiple shocks delivered at regular intervals of 120 s. Fear memory retrieval was assessed on days 1, 7, and 14 following conditioning. Calcium imaging was used to analyze neuronal activity in the PFC from which we divided PFC neurons into three disjoint groups as follows: Group 1 (G1) included neurons that exhibited immediate responses to shocks (i.e., shock cells). Group 2 (G2) included neurons that displayed strong connectivity with G1 during conditioning (correlation coefficient > 0.5). Group 3 (G3) included the remaining neurons. Then, we constructed a network combining all these groups together and evaluated the network properties of degree of connectivity and centrality for each neuron, which could indicate the importance of single neurons to transfer information through the network. During the habituation phase, G1 and G2 exhibited high centrality, whereas G3 exhibited low one. Among the groups, G2 showed the highest degree of connectivity. Then, this pattern was altered such that the centrality and degree of connectivity of G1 and G2 decreased whereas those of G3 increased over days during memory retrieval assessment. Furthermore, the overall degree of connectivity peaked on day 1, then decreased on the following days. These changes in network properties of each group may suggest a reorganization of

networking among PFC neurons, presumably related to changes in inter-regional connectivity of PFC and other brain regions. Further studies on underlying mechanisms of the network reorganization of PFC neurons in fear memory consolidation should follow to help us understand the implications of intra-regional networks of PFC in memory formation.

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Poster

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Topic: H.08. Learning and Memory

Support: NRF-2019M3E5D2A01058328
NRF-2021M3E5D2A01019544
HU20C0233

Title: Decoding of remote fear memory from ensemble activity in prefrontal cortex

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Abstract: The prefrontal cortex (PFC) has been proposed to play a role in both the consolidation and retrieval of long-term memory. However, how memory consolidation and retrieval are represented in ensembles of PFC neurons is poorly understood. In order to investigate this question, we performed *in vivo* Ca^{2+} imaging in ensembles of excitatory neurons in PFC under the contextual fear conditioning (CFC) paradigm, and memory retrieval was tested on day (D)1, D7, and D14 after CFC to test recent (D1) and remote (D7, D14) memory retrieval in C57BL/6J mice. During conditioning, we observed that excitatory neurons in the prefrontal cortex (PFC) could be divided into two subpopulations of shock-responsive (SR) and non-responsive (SNR) cells. Although there were no significant differences in the calcium activity of the two subsets of neurons on D1 and D7, there was an increase in the calcium event frequency of shock-responsive (SR) cells on D14. Furthermore, training a support vector machine (SVM) using SR cells and predicting the behavior state (Freezing/Unfreezing) resulted in a progressive increase in decoding performance after conditioning, enabling successful prediction of mice behavior by remote recall, while the decoder trained using SNR cells consistently performed below the null model. Together, these results indicate that the PFC SR cells are an important substrate for the retrieval of remote contextual fear memory.

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Poster

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Topic: H.08. Learning and Memory

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NIH R56MH113894

Title: Neocortical synaptic engrams for remote contextual memories

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Abstract: While initial encoding of contextual memories involves the strengthening of hippocampal circuits, these memories progressively mature to stabilized forms in neocortex and become less hippocampus dependent. Although it has been proposed that long-term storage of contextual memories may involve enduring synaptic changes in neocortical circuits, synaptic substrates of remote contextual memories have been elusive. Here we demonstrate that the consolidation of remote contextual fear memories in mice correlated with progressive strengthening of excitatory connections between prefrontal cortical (PFC) engram neurons active during learning and reactivated during remote memory recall, whereas the extinction of remote memories weakened those synapses. This synapse-specific plasticity was CREB-dependent and required sustained hippocampal signals, which the retrosplenial cortex could convey to PFC. Moreover, PFC engram neurons were strongly connected to other PFC neurons recruited during remote memory recall. Our study suggests that progressive and synapse-specific strengthening of PFC circuits can contribute to long-term storage of contextual memories.

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Poster

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Topic: H.08. Learning and Memory

Support: National Institute of Mental Health of the National Institutes of Health under Award Number R01MH123687

Title: Learning of the Latent Structure of Object Relationship in Rhesus Monkeys

Authors: *X. WEN[1], S. DHUNGANA[2], A. NEUMANN[2], M. WATSON[2], T. WOMELSDORF[2];
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Abstract: Learning the latent structure of information is a key process to enhance flexible and intelligent cognition. The benefits of learning latent structure become evident in the spatial domain when subjects flexibly navigate learned spatial maps despite new obstacles or when subsections within the map change. Similar benefits of latent-structure learning are likely evident in the object domain, but it has remained unclear how subjects benefit from learning the latent relationships of objects. Here, we hypothesized that learning the latent temporal relationship of objects facilitates flexible adjustment to changing object relationships, reduces interference from distracting objects, and enhances long-term retention of relevant objects.
To test these hypotheses, we trained nonhuman primates (NHP's) to learn object sequences and then (i) introduced distracting objects to quantify how learned structure reduces interference, (ii) swapped the order of objects to quantify how fast subjects adjust to changes of learned latent structures, and (iii) repeated learned sequences to test whether long-term retention is enhanced when abstract object relationships have been learned. NHP's performed the object-sequence task at touchscreen Kiosk stations with multidimensional objects. Each sequence consisted of five sequence-relevant objects and one sequence-irrelevant distractor that was similar to only one of the sequence-relevant objects. After incorrect choices the display was reset with new, random object positions to ensure an object-based and prevent a spatial-based learning strategy. Each object sequence was repeated once with swapped object order, and it was repeated once more later in the session to test long-term retention.
We found that NHPs rapidly learn sequences of five objects with above-chance performance. Learning speed improved for object-sequences that contained objects with swapped position, indicating that the abstract temporal ordering of objects was learned. The distractor object caused less interference in sequences that contained swapped objects and that were repeated later in the session. Finally, NHP's showed a long-term memory advantage evident in faster learning of sequences that repeated after twelve or more intervening sequences.
Taken together, these results suggest that NHPs rapidly learn abstract sequential relationship of objects and leverage the learned latent structure to reduce interference, enhance flexible adjusting to changing structures, and for improving long-term retention.

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Poster

PSTR302. Prefrontal Cortex Networks and Behavior

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Topic: H.08. Learning and Memory

Support: J. Douglas Tan Postdoctoral Fellowship
Simons Postdoctoral Fellowship

Title: Multi-agent evidence accumulation in the anterior cingulate cortex of monkeys

Authors: *R. CHEN[1,2,3], N. VALLURU[1,2,3], S. M. YOO[1,2,3], S. RADKANI[1,2,3], M. JAZAYERI[1,2,3];
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Abstract: When making decisions under uncertainty, humans and animals combine evidence from their own experience with that of others. For example, when choosing which restaurant to dine in, we may combine information from our last visit with testimonials from others. However, animal experiments where precise neural measurements are feasible have largely focused on evidence accumulation from self-experience only. Therefore, the neural basis for multi-agent evidence accumulation is not known. The anterior cingulate cortex (ACC) has been implicated in a variety of cognitive and social processes, including hierarchical decision making, conflict monitoring, and reward-monitoring for self and other agents. Here, we investigated the role of ACC in multi-agent evidence accumulation. We recorded simultaneously from ACC of two monkeys, sitting next to each other, while they played a virtual hunting game. The game was designed such that animals could benefit from integrating evidence across experiences of self and other. Each trial consisted of two phases. In phase 1, both animals were presented with two arenas and each made a choice between them. On every trial, only one arena could yield reward, and the correct option changed covertly after 12-25 trials. As such animals had to choose judiciously using evidence from previous trials. In phase 2, one monkey was randomly assigned as the “actor” and had to hunt preys in its chosen arena (i.e., use a joystick to intercept dropping tokens), while the “observer” watched. The actor could receive reward only if it had chosen the correct arena with a probability that increased with the number of captured preys. The observer received no reward but could observe the actor playing and the trial outcome. Behavioral analyses indicated that animals were able to integrate evidence across trials both based on their own experience and the experiences of the other animal. Specifically, animals' arena choices were sensitive to the history of their own choices and outcomes as well as those of the other animal. ACC neurons were strongly modulated by behaviorally relevant task variables for both self and other including choice of arena, inter-agent choice conflict, and reward outcome. In both animals, patterns of activity across the population of neurons (i.e., encoding axis) reflected the cumulative evidence based on the history of outcomes for self and other. Notably the axes of evidence accumulation between self-experience and observed other-experience were aligned and overlapping. These findings suggest that ACC may support decisions that rely on information gathered from experiences of multiple agents.

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Poster

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Topic: H.08. Learning and Memory

Support: NRF-2019M3C1B8090805
2022R1A2C2005062
NRF-2022R1I1A4063209

Title: Optogenetic stimulation of mPFC modulates sleep in Sprague-Dawley rats

Authors: *Y. LEE[1], Y. LEE[2], S. HWANG[3], H. LEE[4], S. JUN[3];
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Abstract: Several studies have been conducted to improve the quality of sleep using brain stimulation. It is well known that the quality of sleep is related to the sleep depth, duration, onset latency, and the ratio of non-rapid eye movement (NREM) sleep to rapid eye movement (REM) sleep. In particular, sleep spindle and slow wave in the electroencephalography (EEG) during NREM sleep are regarded as important factors for cognitive functions. Sleep spindles are implicated in long-term potentiation for memory consolidation and slow wave is shown to play an important role in the reinforcement of memory. In order to modulate sleep, accordingly, many studies attempted the stimulation of thalamic reticular nucleus (TRN) which is known to be origin of sleep spindle. However, TRN is located in the deep brain region, making it challenging for clinical use. In this study, medial prefrontal cortex (mPFC) was chosen as a target brain area of optogenetic stimulation because mPFC forms a cortical-thalamic network, a major neural circuit involved in sleep-awake control by oscillating neural signals with TRN and thalamus. Three different frequencies of light stimulation were attempted to Sprague-Dawley rats expressing channelrhodopsin-2 (ChR2) in the mPFC region. First, 2 Hz (50 % duty cycle) was applied to induce slow wave. Second, 10 Hz (50 % duty cycle) was applied for REM sleep control and the effect was previously demonstrated. Third, spindle-like stimulation was used to increase sleep spindle. The protocol for spindle-like stimulation contains light pulses (62 ms duration) at 8 Hz which is the intrinsic frequency of sleep spindles, and the stimuli were repeated at 0.5 s intervals which is the average interval between sleep spindles. EEG and electromyography (EMG) signals were recorded for one hour as a baseline, one hour during the optogenetic stimulation period, and six hours as a post-stimulation period. Power spectrum analyses of EEG and EMG were performed to estimate sleep stages. The delta power of EEG was obtained as a measure of deep sleep and sleep spindles were detected as an indicator of long-term memory consolidation. Additionally, the Y-maze test was conducted to evaluate the cognitive enhancement. As a result, this study verified that optogenetic stimulation of mPFC can effectively modulate sleep patterns, leading to improved sleep quality as well as cognitive function.

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Poster

PSTR302. Prefrontal Cortex Networks and Behavior

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.18/VV40

Topic: H.08. Learning and Memory

Support: IBS-R002-A1

Title: Roles of intratelencephalic and pyramidal tract neurons of the prefrontal cortex in probabilistic reversal learning

Authors: *Y. YOON[1,2], J. YI[2], S. JUNG[1,2], M. JUNG[1,2];
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Abstract: The prefrontal cortex (PFC) is known to play a crucial role in flexible control of behavior. To investigate roles of intratelencephalic (IT) and pyramidal tract (PT) neurons of the PFC in flexible control of behavior, we performed optogenetic modulation and calcium imaging of these neurons in deep layers of the medial PFC (mPFC) in adult mice engaged in a probabilistic classical conditioning task with cue-outcome contingency reversal. Our preliminary findings suggest that the effect of optogenetic modulation on behavior and neural activity dynamics during reversal learning differ between IT and PT neurons. Optogenetic inhibition of PT neurons, but not IT neurons, tended to increase the number of trials to reach the reversal criterion. Calcium imaging revealed that many PT neurons maintained cue- and expected outcome-dependent activity, but the majority of IT neurons displayed complex activity dynamics during the progress of behavioral reversal. Also, only the PT neuronal population showed an abrupt change in punishment-related responses following reversal onset. Although further studies are needed to determine specific functional roles of these cell types in probabilistic reversal learning, our findings so far suggest a more direct involvement of PT than IT neurons.

Disclosures: Y. Yoon: None. **J. Yi:** None. **S. Jung:** None. **M. Jung:** None.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR302.19/VV41

Topic: H.08. Learning and Memory

Title: Differences In Prefrontal Cortex During Recall Due To Sample-Match Discordance

Authors: *B. M. ROEDER[1], M. R. RILEY[2], R. E. HAMPSON[2];
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Abstract: The Prefrontal Cortex (PFC) region of the brain is involved in the recall of images and where computations of relevant task-related information (i.e. “Matched” compared to “Not Matched”). Other brain areas of the Papez memory circuit exert a modulatory control on hippocampal-prefrontal communication via hippocampal connections, leading to gating of information and a way to compare expected vs. actual information processed by the memory circuit, however there still remains a question as to whether a similar influence is exerted on the PFC. Our study aimed to determine if such an effect is present.

To test this influence, we used a delayed-match-to-sample (DMS) task. In the sample phase of the DMS task, a sample image is presented to the subject on a touch screen, where the subject responds by touching the image. Upon response, the sample image disappears and a delay of 9 to 11 seconds occurs before the match phase begins. The match phase consists of 1 matching image and 3 non-matching images. The subject successfully completes the trial by touching the correct matching image. Half of the trials used normal match and non-match images, while the remaining trials used distorted match and non-match images. Each unique sample image was used twice, once in a trial with normal match and non-match images and once in a trial with distorted match and non-match images. The trials were arranged so that half of the sample images had their trial with normal images precede the trial with distorted images, and the remainder sample images had the trial with distorted images precede the trial with normal images. This allowed for investigation into how differences between sample and match images can influence recall, but also to determine if later trials were influenced by previous trials with the same sample image.

Early results showed both an increase and decrease in activity within session, which suggests that there is a difference in recall when there is a mismatch between the sample and match image. As such, our data suggest that the PFC may be influenced by other brain areas of the circuit during recall similar to the hippocampus.

This better understanding of how mismatches lead to *differential* encoding and recall will lead to a better understanding of how that information is remembered. In addition, additional work on how prior memories influence later ones will assist in the development of treatments and devices to assist not only storage and recall for Alzheimer’s Disease and brain injury, but also how to “filter” human memory to reduce the impact of abnormal or intrusive memories such as those involved in PTSD, drug abuse relapse, and psychological health disorders.

Disclosures: **B.M. Roeder:** None. **M.R. Riley:** None. **R.E. Hampson:** None.

Poster

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Topic: H.08. Learning and Memory

Support: Israel Science Foundation (770/17)
NIH-BSF CRCNS (2019793)

Title: Characterization of neural processes involved in flexible discrimination learning in a value-based decision making task using functional magnetic resonance imaging in mice

Authors: *D. LICHTMAN[1,2], E. BERGMANN[1,2], D. RINBERG[3], I. KAHN[1];
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Abstract: One of the fundamental aspects of the process of memory is the ability to learn from experience and hence guide value-based decisions. While these cognitive processes are studied extensively in humans using fMRI, characterization of brain-wide networks in the behaving rodent remains a major challenge. We evaluated the neural processes implicated in learning from the naïve state to task proficiency in the mouse by combining fMRI, precise odor delivery system and high-resolution behavioral monitoring of sniff and lick behaviors. In a task that combined a Go/No-go odor discrimination learning phase and subsequent to it a reversal of odor association with responses, we sought to identify the brain structures that contribute to the formation and reformation of lick responses to a target odorant. We found that whole-brain responses to correct behavioral responses in Go trials (Hits) showed an opposite neural response between the striatal and hippocampal memory systems, along with motor control and reward-processing responses in cortical (infralimbic and orbitofrontal cortices) and subcortical regions (nucleus accumbens and amygdala). Furthermore, mice displayed rapid reversal learning of the association between odor stimuli and reward, showing brain-wide neural responses. Current analyses aim to identify brain targets that are potentially necessary for this process, which in future experiments will be tested for causality using chemogenetic and optogenetic control. Further, using models of decision-making, we will test the extent to which neural responses in specific structures follow predicted learning patterns. Collectively, this approach will serve to enable whole-brain monitoring of learning processes which will enable the study of the nature of neural responses underlying complex behavior.

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Poster

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.21/VV43

Topic: H.08. Learning and Memory

Support: Simons Center for the Global Brain

Title: Interactions between visual short- and long-term memory in the primate brain

Authors: *A. PICCATO, M. JAZAYERI;
Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Primates exhibit a rich repertoire of behaviors dependent on visual memory, or memory of objects and their locations. Visual memory spans multiple timescales - visual short-term memory (vSTM) stores information on the order of seconds, and is critical for perceptual decision-making. Visual long-term memory (vLTM) stores information over much longer timescales, and is the basis of our knowledge of the visual world. Functional and anatomical distinctions between these two types of memory have inspired cognitive models of memory in which vLTM and vSTM are considered dependent on distinct retrieval and storage mechanisms. However, the presence of two memory systems does not imply that they do not interact during visual memory-guided behavior. For example, short-term retention of a name is likely easier if it is the same as that of a close friend. Recent behavioral and imaging experiments in humans suggest that there may be interactions between the mechanisms underlying memory at these two timescales. We have designed a novel behavioral paradigm suitable for rhesus macaques to examine the impact of vLTM on vSTM and its neural basis. An animal has to make a memory-guided saccade to a peripheral location associated with a centrally-cued object. Critically, information about the peripheral location must be retrieved from either vSTM or vLTM. Congruent vSTM trials, requiring retrieval of an object-location association previously encoded in vLTM, are randomly interleaved with incongruent vSTM trials. This task thus allows us to rigorously test for interactions between memory systems by controlling the congruence of information between these two systems on a trial-by-trial basis. We have trained one monkey on the task, and verified that the animal is able to rapidly acquire multiple sets of visuospatial object-location associations within a single session and accurately retrieve from either vLTM and vSTM. Notably, retrieval was more accurate for congruent trials compared to incongruent trials. Previous work has implicated the dorsolateral prefrontal cortex (dlPFC) and hippocampus (HC) in storage of information over short- and long-term timescales, respectively. We have begun recording the activity of neurons in dLPFC while an animal performs the task. Preliminary data suggests that, when controlling for stimulus identity and target location, activity in dlPFC is modulated by type of memory retrieval (vSTM or vLTM). Activity on vSTM trials is also dependent on whether this information was previously encoded in vLTM (congruence). We plan to continue recording from HC and dlPFC to characterize interactions between long- and short-term memory in these regions.

Disclosures: **A. Piccato:** None. **M. Jazayeri:** None.

Poster

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Topic: H.08. Learning and Memory

Support: NRF-2020M3E5D9080734

Title: Early growth response protein 2 signaling modulates stress resistance function in the medial prefrontal cortex

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Abstract: Early growth response protein 2 (EGR2) is an immediate early gene and transcription regulatory factor that contains three zinc fingers. EGR2 mRNA and protein are observed in various brain regions, including the neocortex, hippocampus, amygdala, olfactory bulb, striatum, cerebellum, and brainstem. Decreased levels of EGR2 have been reported in the dorsolateral prefrontal cortex (dPFC) of patients with post-traumatic stress disorder (PTSD). Rats with lesions in the medial prefrontal cortex (mPFC) exhibited decreased resistance to stress. Therefore, we investigated the impact of down-regulating EGR2 in the mPFC on resistance to stress-induced cognitive impairment. Rats with viral-mediated knockdown of EGR2 in the mPFC were subjected to either a brief 20-min restraint plus 20 intermittent tail shocks (20-min stress), which did not induce memory impairments, or a prolonged 60-min restraint plus 60 intermittent tail shocks (60-min stress), resulting in memory impairment. The cognitive status of these stressed rats was assessed using a novel object recognition task. Control rats showed intact recognition memory following 20-min stress and impaired memory following 60-min stress. However, rats with EGR2 knockdown in the mPFC displayed impaired recognition memory after experiencing 20-min and 60-min stress. Subsequently, we investigated the effect of EGR2 overexpression in the mPFC on stress resistance. When EGR2-overexpressing rats underwent 20-minute stress, recognition memory was similar to the control (empty vector) group. However, the control group that received 60-min stress displayed cognitive impairment, while the overexpression group showed no memory impairments. Our findings suggest that EGR2 signaling in the mPFC is crucial in modulating stress resistance. Dysregulation of EGR2 signaling may contribute to the development of stress-related psychiatric disorders, but overexpression of EGR2 could represent a novel therapeutic approach for the recovery of cognitive function.

Disclosures: **Y. Jeon:** None. **N. Kim:** None. **Y. Jang:** None. **J. Han:** None.

Poster

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Title: Phasic cholinergic modulation of medial prefrontal cortex during learning under uncertainty

Authors: *G. TU[1,2,3], P. WEN[3], K. TAKEHARA-NISHIUCHI[3,4,2];
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Abstract: Anticipating future uncertain threats and making adaptive decisions are crucial for surviving in an ever-changing world for animals. Theory posits that neuromodulators play essential roles in uncertainty estimate and posits their influences on learning and decision-making. In particular, acetylcholine modulates sensitivity to the known unreliability of predictive relationships among cues, actions, and outcomes (expected uncertainty) (Yu and Dayan, 2005). In the mammalian brain, basal forebrain (BF) cholinergic neurons provide the major acetylcholine input to the entire cortex and show transient activation upon threats within milliseconds (Hangya et al., 2015). It led us to hypothesize that threat-evoked phasic cholinergic signaling might provide uncertainty-related information to cortical regions for processing future uncertain threats. To address this, we manipulated BF cholinergic terminals activity in one of the efferent targets, medial prefrontal cortex (mPFC), a region critical for adaptive threat anticipation, in a probabilistic spatial learning task. In this task, mice received probabilistic delivery of air puffs midway when traversing one of two paths in a square maze. Male ChAT-IRES-Cre mice (C57B6J) were injected with adeno-associated viral vectors carrying channelrhodopsin (ChR2 or its red-shifted version, ChrimsonR), or yellow fluorescent protein (control) in a Cre-recombinase-dependent manner. When air puffs were delivered 25% of the time in one path and 75% in the other, control mice preferentially chose the path associated with lower puff probability. However, optogenetically enhancing cholinergic terminals activity during air puffs abolished choice preferences in ChR2 and ChrimsonR mice. In contrast, the same manipulation did not affect adaptive path selection when air puffs were delivered in one path but not in the other path, highlighting an exclusive involvement of phasic cholinergic signaling in learning under uncertainty. Furthermore, we monitored mPFC pyramidal neuronal activity with genetically encoded calcium indicator GCaM6f and applied simultaneous optogenetic stimulation to the cholinergic terminals (inscopix nVoke2 system). Imaging data showed that mPFC neurons activity changed upon air puffs delivery and were sensitive to air puffs probability in each path. However, cholinergic terminal stimulation disrupted such activation in the mPFC network. Together, these data suggest that threat-evoked phasic cholinergic signaling enables mPFC to incorporate uncertainty into threat coding, thereby supporting the development of adaptive threat anticipation sensitive to threat probability.

Disclosures: G. Tu: None. **P. Wen:** None. **K. Takehara-Nishiuchi:** None.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.24/Web Only

Topic: H.08. Learning and Memory

Support: CFI Leaders Opportunity Fund
NSERC Discovery Grant RGPIN-2015-04479
NSERC Alexander Graham Bell Doctoral Award CGSD3-504498 -2017

Title: Distributed representations of time-linked memory in rat medial prefrontal and lateral entorhinal cortex

Authors: *M. PILKIW[1,2], M. D. MORRISSEY[1,3], K. TAKEHARA-NISHIUCHI[1,3,2,4]; [2]Cell and Systems Biol. Dept., [3]Psychology Dept., [4]Neurosci. Program, [1]Univ. of Toronto, Toronto, ON, Canada

Abstract: Many cognitive functions, such as episodic memory and decision-making, rely on the ability to associate an environmental stimulus with a salient outcome over a temporal gap. An established paradigm to study this time-linking process is trace eyeblink conditioning. In this paradigm, subjects are presented with pairings of a neutral conditioned stimulus (CS) and an aversive electric stimulation to the eyelid (US), separated by a stimulus-free period called trace interval. The acquisition and expression of the CS-US association depend on the integrity of the medial prefrontal cortex (mPFC, Takehara-Nishiuchi et al., 2005) and the lateral entorhinal cortex (LEC, Tanninen et al., 2015). Parallel investigations on spiking activity found selective firing patterns for the CS-US association in both regions (Morrissey et al., 2017; Pilkiw et al., 2017). To uncover the specific roles these regions play in representing the CS-US associations, the present study directly compared the information represented in firing patterns during the trace interval in the mPFC and LEC. A support vector machine classifier was trained to differentiate population firing rates (pFR) during four task phases, before the CS, during the CS, trace interval, and after the US. With pFRs from both regions, the classifier successfully discriminated pFRs during the trace interval from those during the other phases. However, the decoding accuracy was higher with mPFC pFRs than with LEC pFRs. With LEC pFRs, most errors originated from confusion between the trace interval and the CS. In contrast, with mPFC pFRs, errors were due to misclassifications of the trace interval as the US. In addition, when a classifier was trained with pFRs during trials with one CS and tested on those during trials with a different CS, decoding accuracy was dramatically decreased in the LEC but was not affected in the mPFC. These findings suggest that the LEC maintains accurate representations of stimuli after they have terminated, whereas the mPFC converts the stimulus information into expectation signals for the imminent outcome.

Disclosures: M. Pilkiw: None. **M.D. Morrissey:** None. **K. Takehara-Nishiuchi:** None.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.25/VV46

Topic: H.08. Learning and Memory

Support: NIH Grant 5U01NS121472

Title: Single neuron representations of sequential task structure emerge rapidly in human anterior cingulate and entorhinal cortex

Authors: *H. AZAB[1], M. EL-GABY[2], S. SHAH[1], R. MATHURA[1], E. BARTOLI[1], A. WATROUS[1], A. ANAND[1], J. ADKINSON[1], T. DONOGHUE[4], S. M. PERREIRA[4], U. TOPALOVIC[5], J. SAKON[5], Z. KURTH-NELSON[6], E. SMITH[7], N. SUTHANA[5], I. FRIED[5], J. JACOBS[4], M. BOTVINICK[6], T. E. J. BEHRENS[3], S. A. SHETH[1];
[1]Baylor Col. of Med., Houston, TX; [2]Univ. of Oxford, [3]Univ. of Oxford, Oxford, United Kingdom; [4]Columbia Univ., New York, NY; [5]Univ. of California Los Angeles, Los Angeles, CA; [6]DeepMind, London, United Kingdom; [7]Univ. of Utah, Salt Lake City, UT

Abstract: Humans have the remarkable ability to take a sequence of verbal instructions and rapidly "program themselves" to execute this new task at a high degree of accuracy. How is this remarkable flexibility implemented in the brain? To explore this question, we asked patients in the Epilepsy Monitoring Unit (EMU) to perform a spatial sequence memory task for the first time while we recorded single-neuron activity in multiple prefrontal and mediotemporal brain regions. Patients had to find and remember the spatial locations of four hidden goals on a 2D grid displayed on a computer monitor, and then visit these goals repeatedly in sequence. After several sequence repetitions, the locations of the goals change, and patients had to find and cycle through the new locations. This was repeated 24 times with 6 unique goal layouts. We have recorded data from 11 patients in 14 behavioral sessions so far.
We find encoding of progress towards a goal in single neurons in the pregenual anterior cingulate ($n = 5/9$ neurons, $p < 0.0001$) and entorhinal cortex ($n = 7/56$ neurons, $p = 0.021$). These representations appear to remap as the goals change location, where a cell's peak in activity indicated the same level of progress, albeit towards a different goal, with different goal layouts. These representations look very similar to those found in the analog to the pregenual anterior cingulate in the mouse (unpublished data from Timothy Behrens' lab). This similarity is despite the fact that mice take weeks to train on this task, while human patients perform it within a few minutes of reading the instructions and at a higher degree of accuracy.
We also find encoding of the currently-sought goal in the entorhinal cortex ($n = 10/56$ neurons, $p = 0.00042$). This variable is significantly decodable from the entorhinal population, independent of the spatial locations of the goals (6-fold cross validation, $p < 0.0001$). Future work will elucidate how the role of these two representations in rapidly learning and performing the task.

Disclosures: H. Azab: None. **M. El-Gaby:** None. **S. Shah:** None. **R. Mathura:** None. **E. Bartoli:** None. **A. Watrous:** None. **A. Anand:** None. **J. Adkinson:** None. **T. Donoghue:** None. **S.M. Perreira:** None. **U. Topalovic:** None. **J. Sakon:** None. **Z. Kurth-Nelson:** None. **E. Smith:** None. **N. Suthana:** None. **I. Fried:** None. **J. Jacobs:** None. **M. Botvinick:** None. **T.E.J. Behrens:** None. **S.A. Sheth:** None.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.26/VV47

Topic: H.08. Learning and Memory

Support: NIH-R01MH111703

Title: Behavioral and neural correlates of superstitious learning during transitive inference learning in nonhuman primates

Authors: *Y. JIN[1], F. A. MUNOZ SILVA[1], G. G. JENSEN[3], J. GOTTLIEB[1], V. P. FERRERA[2];
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Abstract: Complex environments offer multiple learning opportunities thus posing a "strategic planning" dilemma - the need to choose how to allocate cognitive resources to a given aspect of the environment at any given time point. The normative solution to this problem is based on learnability, with the prior belief that an informative structure exists and can be successfully learned. However, it is unknown whether or how animals estimate learnability in novel and complex environments. Here, we show that nonhuman primates (NHP) infer fictitious structure in objectively random events. We used a transitive inference task in which NHP repeatedly visually interacted with two sets of pictorial stimuli: a "learnable" set in which pictures were assigned cardinal orders and monkeys were rewarded for saccading to the higher-rank stimulus, and an "unlearnable" set in which stimuli were unordered and feedback was either random or actively discouraged consistent choices. The NHP learned the implicit order of the learnable set, but also behaved as though some ordering existed in the unlearnable set under both reward schedules. The behavior was not explained by model-free Q-learning algorithms, suggesting that fictitious ordering reflected an internal representation of stimulus order. Neurons in the dorsal anterior cingulate cortex (dACC, 24c, N=50) presented responses predominantly during choice selection or after feedback delivery and encoded learnability, reward value, and their interaction. Particularly during the second half of the session when behavior was more stabilized, many neurons (47.1%) encoded both the objective rank and prediction error in the learnable context and the fictitious rank and subjective prediction error in the unlearnable context. These results suggest that dACC may support diverse learning strategies when facing environments with mixed learnabilities.

Disclosures: Y. Jin: None. **F.A. Munoz Silva:** None. **G.G. Jensen:** None. **J. Gottlieb:** None. **V.P. Ferrera:** None.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.27/VV48

Topic: H.08. Learning and Memory

Support: NSF Grant 62293550
NSF Grant 62293551
NSF Grant 61977008

Title: Shared representation of conceptual knowledge among students during classroom teaching

Authors: *X. FENG, X. XU, Y. WANG, C. LU;
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Abstract: Shared representation of conceptual knowledge among students duringclassroom teachingAuthorsXiaodan Feng, Xinran Xu, Yangchunxiao Wang, Chunming Lu*; State Key Laboratoryof Cognitive Neuroscience and Learning and IDG/McGovern Institute for BrainResearch, Beijing Normal University, No.19 Xinjiekouwai Street, Beijing 100875, PRChina;**DisclosuresXiaodan Feng:** None. **Xinran Xu:** None. **Yangchunxiao Wang:** None. **ChunmingLu:** None.**Acknowledgements:** This work was supported by the National Natural ScienceFoundation of China (62293550, 62293551, 61977008).**Abstract**Previous extensive studies have been conducted on the cognitive and neuralrepresentation of conceptual knowledge at the individual level. However, little isknown about how conceptual knowledge is represented among individuals duringteaching in the classroom, and how learning tyles modulate the cognitive and neuralrepresentations. To address this issue, an integrated functional near-infraredspectroscopy hyperscanning system with 21 nodes was employed to measurechanges of hemoglobin concentrations from 21 students while an active or a passivelearning occurred during classroom teaching. By vectoring the takeaways using theLatent Dirichlet Allocation model and transforming semantic representations intonetworks of takeaways, we found the stronger the semantic connections a takeawayhas with other takeaways, it is better to be remembered. Next, to understand theneural representation, a representational similarity analysis was conducted betweenbrain activity pattern and takeaways annotations. The results indicated that, whileshared neural representation was found in the angular gyrus during passive learning,no consistent pattern was found among students during active learning, suggesting adeep processing of knowledge through subjective construction during activelearning. Additionally, we found that after a passive learning that immediatelyfollowed the active learning, a significant shared neural representation appeared inthe middle frontal cortex. We also asked the students to perform an active learningimmediately after a passive learning. Again, a significant shared neuralrepresentation was found in the MFC. Together, these results suggested that theshared representation of conceptual knowledge was associated with the knowledgehierarchy. While passive learning was associated with the shared representation ofshallow semantics, active learning was associated with the deep semanticsaccessed through subjective construction probably based on individual's priorknowledge.**Keywords**
Active learning; fNIRS; Knowledge representation

Disclosures: X. Feng: None. **X. Xu:** None. **Y. Wang:** None. **C. Lu:** None.

Poster

PSTR302. Prefrontal Cortex Networks and Behavior

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR302.28/VV49

Topic: H.08. Learning and Memory

Support: National Science Foundation BCS-2043740 (M.D.R.)

Title: Functional brain network predictors of surprise in controlled task and naturalistic viewing contexts

Authors: *Z. ZHANG[1], M. D. ROSENBERG[2];
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Abstract: Functional brain network predictors of surprise in controlled task and naturalistic viewing contexts
Our environment is always changing. To navigate the world around us, we generate predictions, form beliefs, and learn from surprising changes that violate our beliefs, such as when objects move abruptly or people behave unpredictably. What are the brain networks that predict this experience of surprise in a complex environment? To address this question, we reanalyzed openly available fMRI data collected as participants performed a task in which they learned to predict the location of an upcoming object (N=32; McGuire et al., 2012; Kao et al., 2020). McGuire et al. (2012) developed a normative model tracking *surprise* (changes in the mean of an occluded generative distribution of the object's location) and *uncertainty* (about the generative mean) in this task. To identify functional brain networks whose strength predicted these measures, we calculated the co-fluctuation time course (Faskowitz et al., 2020, Zamani Esfahlani, 2020) of all pairs of 268 brain regions in a functionally defined atlas as the product of their *z*-scored BOLD-signal time series. Using leave-one-subject-out cross-validation, we identified region pairs ("edges") whose co-fluctuation varied across trials with normative surprise and uncertainty. These edges predicted surprise and uncertainty in held-out individuals: edges *positively* correlated with surprise were stronger on trials with more unexpected outcomes (mean within-subject rho=0.09; $t(62)$=7.65, p<0.001) whereas edges *negatively* correlated with surprise showed the opposite pattern (mean rho=-0.09; $t(62)$=-7.15, p<0.001). We next asked whether the same edges predicted surprise in a naturalistic context. We measured dynamic changes in these edges in openly available fMRI data collected as novel participants watched NCAA basketball games (N=20; Antony et al., 2021). Edge strength tracked a validated measure of surprise (change in a team's win probability) from basketball analytics. These results suggest that brain dynamics in a common functional network predict surprise in very different contexts.

Disclosures: Z. Zhang: None. **M.D. Rosenberg:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.01/VV50

Topic: H.08. Learning and Memory

Title: Representational drift of contextual fear engrams across the brain

Authors: *T. WANG[1], T. ZHANG[2], B. DUNGATE[2], J. SNYDER[2];
[1]Psychology, [2]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The physical manifestation of memory is an "engram", the population of neurons that is activated during a learning experience and, when reactivated, contributes to the process of memory retrieval and subsequent behaviour (Josselyn & Tonegawa, 2020). Traditionally, it has been believed that neural representations must remain stable to maintain memories (Guzowski et al., 1999; Reijmers et al., 2007). However, memories are dynamic and recent investigations have revealed that neural representations are more fluid than formerly thought. In the hippocampus, a critical structure for daily event memory, neurons previously recruited during an experience show variation through time, a process called representational drift (Sweis et al., 2021). This phenomenon has been overlooked due to limitations in traditional electrophysiological approaches that often only record from identified neurons on a timescale of minutes to hours (Leutgeb et al., 2005). However, modern mouse models (or Ca2+ imaging), which permanently label activated neurons, suggest varying reactivation rates in the hippocampus over days (Ramirez et al., 2015; Redondo et al., 2014). Understanding how representations drift over longer intervals is crucial to comprehending how short-term and long-term memories guide future behaviour. Since perception and memory rely on a myriad of brain regions, and drift has been identified in areas outside of the hippocampus (Rule et al., 2019), it is essential to adopt a broad network-level approach to truly understand the stability of neural representations. Recent research stresses this idea by demonstrating that activity in individual regions fail to correlate with fear memory retrieval (Santos et al., 2021). Here, to characterize representational drift across sensory and associational regions of the brain, FosTRAP2 mice and activity-dependent tagging are used to indelibly label activated neuronal populations during two identical contextual fear conditioning events, at recent and remote timepoints. This work will help to identify the extent to which representations drift in individual brain regions and brain-wide networks that are involved in perception and memory.

Disclosures: **T. Wang:** None. **T. Zhang:** None. **B. Dungate:** None. **J. Snyder:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.02/VV51

Topic: H.08. Learning and Memory

Title: Hippocampal CA2 E/I imbalance in the circuit of cognition and social memory

Authors: *A. FRANZ[1,2], S. JAEGER[2], M. FUNK[2], D. KÄTZEL[1], B. HENGERER[2];
[1]Inst. of Applied Physiol., Ulm Univ., Ulm, Germany; [2]CNS Dis. Res., Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

Abstract: Disturbances in the neuronal activity of the hippocampal CA2 subregion have been shown to result in impaired social memory in rodents. However, the current assessment of behavioural role of CA2 within the circuit of cognition relies on classical tests, presenting only a snapshot of the behaviour of subjects. As both clinical and preclinical data have revealed a relevance for CA2 in psychiatric disorders such as schizophrenia, it is crucial to uncover the effects of CA2 E/I imbalance in more natural social environments over longer periods of time. Furthermore, gaining a deeper understanding of molecular alterations within the underlying circuit of cognition is essential for the development of future therapeutic treatments. To further characterise downstream effects of an E/I imbalance in murine CA2, CA2 pyramidal neurons were chronically silenced using viral-mediated Designer Receptors Exclusively Activated by Designer Drugs (DREADD) expression. During early adulthood, we performed automated behaviour analysis of individuals in social groups using long-term radio-frequency identification (RFID)-supported video tracking. Subsequently, we utilized high-throughput confocal microscopy combined with automated image analysis to investigate molecular effects of CA2 E/I imbalance on key proteins involved in neuronal activity of target brain regions. Our findings provide a detailed examination of the effects of chronic DREADD-mediated CA2 E/I imbalance on several distinct social behaviours during the light and dark cycle. Additionally, our study contributes to a broader understanding of the molecular consequences associated with this imbalance.

Disclosures: **A. Franz:** A. Employment/Salary (full or part-time):; BI Pharma GmbH & Co. KG. **S. Jaeger:** A. Employment/Salary (full or part-time):; BI Pharma GmbH & Co. KG. **M. Funk:** A. Employment/Salary (full or part-time):; BI Pharma GmbH & Co. KG. **D. Kätzel:** None. **B. Hengerer:** A. Employment/Salary (full or part-time):; BI Pharma GmbH & Co. KG.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

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Program #/Poster #: PSTR303.03/Web Only

Topic: H.08. Learning and Memory

Support: PAPIIT-DGAPA-UNAM IN205321
COIC/STIA/8224/2017

Title: Striatal and Hippocampal Learning in Adult mouse Upon Prenatal Exposure to Valproic Acid

Authors: *A. HERNANDEZ[1], E. DELGADO-GONZÁLEZ[1], R. DURAIRAJ[1], D. REYES-HARO[1], A. MARTÍNEZ-TORRES[1], F. ESPINOSA[2];
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Abstract: Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by persistent deficits in social communication and social interaction. Altered synaptogenesis and aberrant connectivity responsible for social behavior and communication have been reported in autism pathogenesis. Autism has a strong genetic and heritable component; however, environmental factors including toxins, pesticides, infection and *in utero* exposure to drugs such as VPA have also been implicated in ASD. Administration of VPA during pregnancy has been used as a rodent model to study pathophysiological mechanisms involved in ASD, and in this study, we used the mouse model of prenatal exposure to VPA to assess the effects on striatal and dorsal hippocampus function in adult mice. Alterations in repetitive behaviors and shift habits were observed in mice prenatally exposed to VPA. In particular, such mice presented a better performance in learned motor skills and cognitive deficits in Y-maze learning frequently associated with striatal and hippocampal function. These behavioral changes were associated with a decreased level of proteins involved in the formation and maintenance of excitatory synapses, such as Nlgn-1 and PSD-95. In conclusion, motor skill abilities, repetitive behaviors, and impaired flexibility to shift habits are associated with reduced striatal excitatory synaptic function in the adult mouse prenatally exposed to VPA.

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Poster

PSTR303. Hippocampal–Cortical Interactions II

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Topic: H.08. Learning and Memory

Support: China Scholarship Council (CSC 202108330031 to YW)

Title: Enhanced temporal memory and diminished temporal compression after slow and fast theta tACS

Authors: *Y. WANG, P. DE WEERD, V. VAN DE VEN;
Univ. of Maastricht, Maastricht, Netherlands

Abstract: Theta oscillations (3-8 Hz) are believed to play a crucial role in supporting episodic memory formation. Rather than a unitary frequency range, theta oscillations may functionally specialize between slow (3 Hz) for short term memory accuracy and fast theta (8 Hz) for other cognitive functions. Several studies have suggested that theta oscillations play a role in temporal memory formation and sequence learning, but this relation remains to be causally tested. Transcranial alternating current stimulation (tACS) offers a way to modulate theta oscillations of the associative memory network to test its involvement in temporal memory. We aimed to test the contribution of slow vs. fast theta stimulation on temporal memory formation. Participants (N=24) completed three tACS sessions in which stimulation was administered during sequence

encoding. In each session, participants were presented with a series of 72 visual objects, each presented within a frame that changed color every eight items, while simultaneously receiving tACS over area P3 at 8 Hz, 3 Hz, or sham. After encoding, participants indicated the serial position (1-72) at which a picture was presented during encoding on a visual analog scale representing the sequence's timeline. We analysed temporal bias - the rated position minus the actual position, with negative (positive) values indicating temporal compression (temporal dilation) - and temporal accuracy - the absolute magnitude of the rated minus actual position - as a function of tACS conditions.Results showed that slow vs. fast theta tACS affected temporal performance in different ways. During sham stimulation, participants consistently showed a temporal underestimation bias (p<0.001) for items presented further away from a change in frame color, compared to items presented at a color change. This finding is reminiscent of temporal compression that has been observed in event segmentation. Notably, 8 Hz tACS (p=0.009), but not 3 Hz (p=0.071), suppressed this temporal bias. Concurrently, slow theta (p=0.003), but not fast theta stimulation (p=0.31) diminished absolute temporal error (i.e., improve temporal accuracy), compared to sham tACS. Our study represents the first application of brain stimulation to test the contribution of theta stimulation on temporal memory, showing evidence for a functional dissociation of slow and fast theta. We think it is possible that our tACS stimulation affected hippocampal function in temporal memory formation. As such, our study contributes to our understanding of the neural mechanisms underlying episodic memory formation.

Disclosures: Y. Wang: None. **P. De Weerd:** None. **V. Van de Ven:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.05/VV53

Topic: H.08. Learning and Memory

Support: SERB

Title: Neural basis of interference between memory-driven perception and ongoing experience

Authors: *M. PRAJAPAT, N. DAS, E. LOBO, P. JAISWAL, B. JAYAPRAKASH;
Ctr. for Neurosci., Indian Inst. of Sci., Bengaluru, India

Abstract: Declarative memories are a collection of everyday experiences and facts that can be stated explicitly. Episodic memories, a sub-class of declarative memories, when retrieved, are accompanied by the perception of the particular episode. Such memory-driven percepts also invoke the emotional states that were experienced during the experience of the event, along with factual and sensory information. In this study, we hypothesized that the hippocampal subfield CA1 is the neural locus of memory-driven perception; when activated, it interferes with normal sensory perception. Any conflict between memory and sensory perceptions creates a perception

of mixed reality, suppressing the behaviours associated with the sensory or memory-based information alone. We used the tet-tag system in transgenic mice and optogenetic tools to capture and reactivate the memory ensembles. Our findings reveal that activation of memory of the training context did not have any effect when mice were tested in the same context, i.e., when no conflict existed between present and past experiences. However, when the mice were tested in a neutral context, the hippocampal activation led to a conflict of information in perceptual space. Cortical areas detect such conflict, and behaviour linked with mixed perceptual reality emerges. These results provide valuable insights into the cognitive processes of memory and perception and how these interact to modulate behaviour. The identification of the hippocampus as the seat of memory-driven perception provides crucial insights into the neural basis of this phenomenon. Moreover, the detection of conflicts between memory and sensory perceptions by the cortex highlights the role of this brain region in shaping and modulating behaviour. The observed behavioural changes, triggered by the presence or absence of conflict detection, emphasize the intricate interplay between memory, perception, and behaviour.

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Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.06/VV54

Topic: H.08. Learning and Memory

Support: The Jean Phillips Shibley Endowment (T.J.G.)
Penn State University (T.J.G.)

Title: Genetic Differences in the Influence of Acute Ethanol on Trace Fear Conditioning in Mice

Authors: S. J. MURRAY, E. HENRY, *S. LOGUE, T. J. GOULD;
Biobehavioral Hlth., Penn State Univ., University Park, PA

Abstract: Ethanol affects both learning and anxiety but effects of alcohol across individuals are not homogenous. Genetic differences and sex are important factors that may contribute to variability in the effects of acute ethanol on learning and anxiety. We were interested in examining genetic differences in fear learning that engages areas sensitive to ethanol. Trace fear conditioning is a type of fear conditioning in which there is a delay between the conditioned stimulus (tone CS) and the unconditioned stimulus (foot shock US). This results in subjects learning a fear association with the context, which involves the hippocampus, and fear association with the tone CS, which because of the delay between CS offset and US onset, engages prefrontal cortex and hippocampus. Both the prefrontal cortex and hippocampus are sensitive to the effects of ethanol. To explore the genetic differences in the effects of acute ethanol on trace fear conditioning, saline, 1.0 g/kg, or 1.5 g.kg ethanol was administered

intraperitonially prior to training in trace fear conditioning in male and female C57BL/6J (B6) and DBA/2J (D2) mice. Fear learning to the context was assessed 24 hr later by measuring the level of freezing when mice were tested for 5 minutes in the training context without other stimuli present. One hour later, fear learning to the tone CS was tested in an altered context for 6 minutes (3 minutes before the tone CS & 3 minutes of tone CS). For context learning, ethanol dose dependently decreased freezing to the context in male and female B6 mice, while both doses of ethanol decreased freezing to the context by the same degree in male and female D2 mice. In the tone CS test, ethanol dose dependently decreased freezing to the tone CS in male and female B6 mice, while both doses of ethanol decreased freezing to the tone CS by the same degree in male and female D2 mice. Sex differences were also detected. These results suggest that acute ethanol has deleterious effects on learning to fear the context and the tone CS in the trace fear conditioning paradigm and genetics and sex may contribute to acute ethanol dose response differences between B6 and D2 mouse strains.

Disclosures: S.J. Murray: None. **E. Henry:** None. **S. Logue:** None. **T.J. Gould:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.07/VV55

Topic: H.08. Learning and Memory

Support: DP1 DA046537

Title: Chronic heroin self-administration impairs hippocampus-dependent short term spatial memory in male and female Long-Evans rats

Authors: *J. G. SEVERINO PEREZ, C. DRESSLER, C. REDDY, M. FUNK, C. TOMAS BALTAZAR, M. JIWANJI, M. E. WIMMER;
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Abstract: There are several comorbidities that arise with substance use disorder, such as sleep disturbances, anxiety, depressed mood, and cognitive deficits. These conditions are not only a consequence of drug use but perpetuate further use as well. There are studies to suggest that cognitive deficits in particular are a direct consequence of drug abuse, and those with poorer cognitive functioning are more likely to drop out of cognitive behavioral therapy focused on relapse prevention. Given the nationwide opioid epidemic that results in about 136 deaths per day, it is imperative that we better understand the cognitive deficits that arise from chronic opioid use. The present study seeks to understand the impact of chronic heroin use on hippocampus dependent memory. Adult male and female Long-Evans rats had daily access to either heroin (0.1 mg/kg/infusion) or sucrose pellets for 15 days on a fixed ratio 1 reinforcement schedule. Following a week of forced abstinence and again at 3 weeks of forced abstinence, all rats underwent an object location memory task. In the object location memory task, subjects

were placed in an arena with a spatial cue on the wall and exposed to two identical objects for three 6-minute training sessions, and after a 30-minute delay, one object was placed in a new location relative to the spatial cue. At 1 week of forced abstinence, sucrose-exposed rats spent significantly more time exploring the displaced object, suggesting that the sucrose-exposed rats had intact object location memory. Heroin-exposed males overall did not spend more time with the displaced object after the 30-minute delay. At 3 weeks of forced abstinence, both heroin and sucrose-exposed males spent significantly more time with the displaced objects after a 30-minute delay. Heroin-exposed females, on the other hand, showed no impairment in short-term spatial memory after 1 week of forced abstinence. Taken together, these data suggest that chronic heroin exposure can result in hippocampus-dependent short term memory deficits in a sex-dependent manner. This model will be the foundation for elucidating circuitry and molecular mechanisms underlying drug-induced cognitive deficits. Because cognitive deficits perpetuate further drug use, this research may serve as a starting point for developing novel therapeutics to ameliorate the deleterious effects of chronic heroin use.

Disclosures: **J.G. Severino Perez:** None. **C. Dressler:** None. **C. Reddy:** None. **M. Funk:** None. **C. Tomas Baltazar:** None. **M. Jiwanji:** None. **M.E. Wimmer:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.08/VV56

Topic: H.08. Learning and Memory

Support: ESYCA2023-116314

Title: Palmitic acid induce inflammation and changes in cognitive performance and anxiety in female mice

Authors: *K. L. MARTINEZ-GONZALEZ;
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Abstract: Neuro-inflammation describes an immune-metabolic disorder of the nervous system can be triggered by certain high caloric nutrients such as palmitic acid (PA). Nutrients (such as free fatty acids) may accumulate in the nervous tissues such as microglia due to excessive positive energy balance. The sustained impaired energy balance may invoke glial cells activation and disproportionate production of reactive oxygen species (ROS). Either the excessive generation of ROS or accumulated free fatty acids, such as palmitic acid (PA) might activate the canonical inflammatory pathways or elicit chronic inflammation of the brain (Ngozi et al., 2021). Chronic inflammation may later degenerate into a myriad of neuro-psychopathologies, including cognitive decline, major depressive disorder, and some neurological diseases. PA allowed us to study of changes in cognitive decline PA-induced neuroinflammation (measured by Object Location Memory Task) in female Balb/c mice. After PA challenge, changes associated with

inflammation due to dietary administration of palmitic acid were observed in long-term spatial memory and anxiety in female mice. Administration of palmitic acid could serve as a model to understand what happens at the cognitive level with the consumption of high-fat diets and then propose some treatment that can reverse the cognitive decline associated with consumption of high-fat diets.

Disclosures: K.L. Martinez-Gonzalez: None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.09/VV57

Topic: H.08. Learning and Memory

Support: FG20621

Title: Monosynaptic rabies viral tracing unveils hippocampal CA1 GABAergic inputs and extensive neocortical inputs to GABAergic interneuron types in the distal dorsal subiculum

Authors: *P. GAO[1], X. XU[2];
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Abstract: The hippocampal formation including the dentate gyrus (DG), hippocampus proper (hippocampus), and subiculum (SUB), plays a crucial role in episodic memory and spatial navigation. While SUB is traditionally considered a relay station between CA1 and downstream regions, emerging evidence indicates that the subiculum possesses unique circuit organizational and functional features distinct from CA1. SUB receives circuit inputs that are not solely dependent on the hippocampus, and it has specific cellular composition and distinct spatial/non-spatial representation. These earlier findings suggest that SUB may have novel cell-type-specific circuit organization that is functionally implicated in learning and memory information processing. However, the subiculum has received considerably less attention compared to the hippocampus, with minimal focus on subicular GABAergic interneurons. Therefore, the objective of this project is to address this research gap by investigating the neural circuit connections of interneurons in the subiculum, specifically focusing on the afferents to the distal part of the dorsal subiculum (dSUB). Using our established monosynaptic rabies virus system, we targeted overall GABAergic cells and three major subtypes: Parvalbumin (PV), Somatostatin (SOM), and Vasoactive intestinal peptide-expressing (VIP) in the dSUB. Our results revealed that GAD2+, SOM+, and PV+ cells in the dSUB receive major inputs from CA1, subiculum, postsubiculum, medial septal diagnal band, thalamus, and entorhinal cortex. All these cell types receive GABAergic long-range inputs from CA1. Notably, GAD2+ cells exhibited significantly more cortical inputs than the other groups, including inputs from the visual cortex, auditory cortex, and parietal cortex. Additionally, we observed that distal dSUB GABAergic cells

received inputs from distal CA1 of the posterior hippocampus, demonstrating a broader connectivity pattern that is different from the canonical topographical connection between CA1 and SUB with proximal CA1 projecting to distal dSUB. Our new circuit mapping findings will help us to better understand the circuit operation basis of specific GABAergic cells in the SUB.

Disclosures: P. Gao: None. **X. Xu:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.10/VV58

Topic: H.08. Learning and Memory

Support: NIH: 1R21EY032381-01

Title: Critical period developmental emergence of oscillatory coupling in the hippocampal-neocortical network

Authors: *L. MA[1], D. KHODAGHOLY[2], J. N. GELINAS[3];
[1]Biomed. Engin., [2]Electrical Engin., Columbia Univ., New York, NY; [3]Neurol., Columbia Univ. Irvine Med. Ctr., New York, NY

Abstract: The mature hippocampal-neocortical system exhibits complex connectivity and is central to multiple cognitive processes, such as learning and memory. Expression and coupling of hippocampal sharp-wave ripples (SWRs) and cortical oscillations facilitate and further differentiate different memory stages. However, precisely coordinated oscillatory activity is not an innate property of nascent neural networks. We hypothesized that hippocampal and cortical oscillations require early developmental interactions to shape large-scale network properties. To test this hypothesis, we performed in vivo electrophysiology on unanesthetized mouse pups during the first three postnatal weeks. We used soft, conformable and implantable interface devices to simultaneously probe the developing hippocampus and neocortex. We found that ripple-band oscillations emerged concurrently in hippocampus and cortex during the second postnatal week. These oscillations robustly recruited local neural firing, and developed temporal coupling patterns. These results suggest the importance of hippocampal-cortical communication in the maturation of neural networks, with implications for memory processes.

Disclosures: L. Ma: None. **D. Khodagholy:** None. **J.N. Gelinas:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.11/VV59

Topic: H.08. Learning and Memory

Support: SERB
IISc Intramural Funds

Title: Role of Parvalbumin interneuron (PV-IN) in memory specificity and higher order association

Authors: *N. DAS[1], M. PRAJAPAT[1], U. PANDEY[1], A. CHAKRABARTY[2], B. JAYAPRAKASH[1];
[1]Ctr. for Neurosci., [2]The department of Organic Chem., Indian Inst. of Sci., Bangalore, India

Abstract: Role of Parvalbumin interneurons (PV-IN) in memory specificity and Higher order association• Authors: Nirupam Das, Utkarsh pandey, Aditya Chakrabarty, Balaji Jayaprakash*. Center forNeuroscience and The department of Organic Chemistry, Indian Institute of Science (IISc)Bangalore:560012• **Disclosure:** Nirupam Das: none, Balaji Jayaprakash: none, Utkarsh Pandey: none, Adityachakrabarty: none.• **Email:** nirupamdas@iisc.ac.in, jbalaji@iisc.ac.in• **Abstract:**Newly encoded information or experiences are stored in the form of memory. Consolidation andretrieval of such memories rely on coordinated neuronal activity within and between different brainregions. Interneurons play a crucial role in gating the signal flow and shaping the network dynamics. PV-IN is one of the most predominant interneurons known to facilitate the development and consolidationof memory. We modulate the activity of PV-IN,and find that PV interneurons modulate the memoryspecificity rather than the ability to retrive the memory. We also found that the PV-IN has a **role in thehigher-order association (HOA)** ,inhibition of PV-IN **blocks the HOA.**We further investigated the HOAphenomenon in APP/PS1 transgenic animals commonly used to study Alzheimer's disease(AD). It is wellknown that the number of PV-IN drastically decreases in 6-9 months old AD animals , however it is notknown if the memory specificity is affected. We used AD mice models and observed that animals could**retrieve the remote contextual memory but were unable to form HOA** compared to non-transgenicanimals. Our study demonstrated the diverse role of PV-IN in retrieving recent and remote episodicmemories and its role in HOA.• **Acknowledgement:** We thank Prof. Santanu Mukherjee (Dept. of Organic Chemistry,IISc) forhelping us with preparation and characterization.

Disclosures: N. Das: None. **M. Prajapat:** None. **U. Pandey:** None. **A. Chakrabarty:** None. **B. Jayaprakash:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.12/Web Only

Topic: H.08. Learning and Memory

Support: CIHR
NSERC

Title: Investigating the long-term evolution of retrosplenial cortex neuronal activity around hippocampal ripples

Authors: *J. KARIMI ABADCHI, R. SUTHERLAND, M. MOHAJERANI;
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Abstract: The activity of neurons, both at individual cells and populations level, undergoes evolution over time even if its associated external variables stay stable. This evolution has been proposed to mediate memory consolidation by facilitating the incorporation of new information into the corpus of previously stored knowledge in the neocortex. Memory consolidation is thought to involve continual interactions between the hippocampus and neocortex during brain offline states when hippocampal ripples occur. Ripples are transient, high-frequency oscillations in the local field potentials (LFPs) recorded from the CA1 subfield of the hippocampus, during which the hippocampal-neocortical interactions are enhanced. Therefore, it is of significance to the field of learning and memory to investigate the long-term evolution of peri-ripple neuronal activity in the neocortex. Such investigations may provide insight into the mechanisms by which neocortical neural networks contribute to memory consolidation which could have implications for treating dementia and Alzheimer's disease. With this in mind, we addressed the abovementioned question by recording the activity of the same population of pyramidal neurons from layers 2/3 of the agranular retrosplenial cortex (aRSC), an association cortex heavily implicated in memory processing, using two-photon calcium imaging across multiple days. Additionally, simultaneous recording of local field potentials in the hippocampus was conducted to detect ripples, enabling us to study the long-term evolution of peri-ripple neuronal activity in the aRSC.

Disclosures: J. Karimi Abadchi: None. **R. Sutherland:** None. **M. Mohajerani:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.13/VV60

Topic: H.08. Learning and Memory

Support: NIH Grant 1R01AG076198-01

Title: Impact of Septal Cholinergic Inhibition on CA1 Oscillations, Spatial Memory, & Exploration

Authors: *D. LAYFIELD, S. BICKFORD, K. MOORE, I. CHOI, B. GREGORY, E. L. NEWMAN;
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Abstract: The medial septum is a critical regulator of the hippocampal network. The majority of cholinergic projections to the hippocampus arise from medial septum. These neurons shift and modulate the hippocampus toward encoding, supporting memory, and learning. These neurons are also theorized to promote exploratory behaviors like rearing. More recent activation studies have found that septal cholinergic neuron activation can support fear learning, enhance theta oscillations, and suppresses sharp wave ripples. However, inactivation studies of septal cholinergic neurons are restricted to permanent lesion studies, leaving it unclear how septal cholinergic disruption may affect hippocampal dynamics and spatial memory. To further elucidate the role of these critical neurons, we selectively optogenetically inactivate the cholinergic neurons of the medial septum while recording oscillations of hippocampal CA1 in awake behaving rats. Septal cholinergic inhibition was timed to different behavioral and task epochs. We find that optogenetic inhibition of septal cholinergic neurons modulates theta and gamma oscillations of CA1 with minimal impact on spatial memory and exploratory rearing behavior. These results are congruent with the theory that medial septal cholinergic neurons are to promote the processing of novel sensory inputs or associations.

Disclosures: D. Layfield: None. **S. Bickford:** None. **K. Moore:** None. **I. Choi:** None. **B. Gregory:** None. **E.L. Newman:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.14/VV61

Topic: H.08. Learning and Memory

Support: BBRF Young Investigator Grant
NIMH: R01MH126105
NIMH: R00MH108719
T32MH015174

Title: Evolution of value representations in medial orbitofrontal cortex with ventral hippocampal inputs for cognitive flexibility in mice

Authors: *K. KUMAR, M. HASANTASH, A. GUNGI, Y. LI, C. ANACKER, K. IIGAYA; Columbia Univ., New York City, NY

Abstract: Acquiring rewards in a complex environment requires identifying relevant features that are predictive of reward within a high-dimensional feature space, and keeping track of changes in this reward contingency across time. However, the neural mechanisms underlying this flexible value computation are not well understood. Here we analyzed neural population dynamics in medial orbitofrontal cortex (mOFC) and ventral hippocampus (vHPC) in mice performing a naturalistic decision making task. The mice must discriminate among multisensory features (e.g., odor, texture, location) and learn the values of these different features which

change over time. For example, animals experienced changes of reward stimulus within the same sensory dimension (e.g., odor A to odor B) and across different sensory dimensions (e.g. odor B to texture A). We developed a novel method, called Representational Evolution Analysis (REA), to examine how the neural representations of feature values evolve across time. Using REA, we found that mOFC dynamically represents the feature value of the environment that the animal decided to act upon, even when the animal made the wrong inference. We also studied how vHPC inputs affect the evolving geometry of feature value representations in mOFC. Our study offers a novel insight into how neural computation underlying flexible value coding supports cognitive flexibility in a complex environment.

Disclosures: **K. Kumar:** None. **M. Hasantash:** None. **A. Gungi:** None. **Y. Li:** None. **C. Anacker:** None. **K. Iigaya:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.15/VV62

Topic: H.08. Learning and Memory

Support: R01NS101108

Title: Assessing learning and memory dysfunction in rodents following traumatic brain injury using a radial arm maze paradigm

Authors: *M. HABIB[1], C. ADAM[3], E. MIRZAKHALILI[1], J. A. WOLF[2];
[2]Neurosurg., [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Univ. of Pennsylvania Neurosci. Grad. Group, Philadelphia, PA

Abstract: Traumatic brain injury (TBI) is known to disrupt cognitive processing, especially learning and memory function. We hypothesize that these disruptions arise from disrupted oscillatory communication in the wider hippocampal network following TBI resulting in spatial and working memory dysfunction. In rats, TBI deficits in the Radial Arm Maze (RAM) have been described following a lateral fluid percussion injury (FPI); however, most studies have focused specifically on learning or memory individually. Here we use an adapted version of the RAM that allows us to assess both learning and memory while rats freely run to investigate TBI-associated dysfunction. To this end, Long-Evans rats are food restricted to 85% bodyweight and are acclimated to the RAM where they collect food rewards at the ends of each of the 8 arms. After acclimation the rats are moved to a 3-arm training phase during which rats use spatial cues in the room to navigate to the same 3 baited arms. To successfully perform this task, rats must remember the 3 baited arms and use spatial cues to navigate to them. During a training session, the rats run up to 30 trials, where one trial is complete when all 3 baited arms are visited. While navigating, possible errors include entering an unbaited arm (reference memory) or re-entering a previously retrieved reward arm (working memory). Once the rats complete a session with >40%

error-free trials, they undergo a reversal, which has 2 components: (1) a pre-probe (testing the previous day's arm configuration) and (2) the reversal itself, where one of the 3 arms remains baited while the other two baited arms change locations. Post-probe sessions (assessing the rat's memory of the new configuration) are performed 50 minutes and 24 hours after learning the new set of arms. Rats are then brought back up to weight before undergoing an FPI (2.1 atm) or sham injury. After recovering, rats are returned to 85% bodyweight and reintroduced to the RAM 7 days post-surgery to assess their memory of the pre-surgery 3-arm configuration. They then undergo five additional reversals at the 8-, 9-, 10-, 17-, and 24-day post-surgery timepoints to assess their ability to learn new spatial configurations and retain/consolidate this information. Preliminary results demonstrate no significant difference in the percentage of error-free trials or number of working/reference memory errors per trial between injured (n=1) and sham (n=2) rats. We will continue to power this study to determine if there are TBI-associated learning/memory deficits in our version of this task and will implant high-density, laminar electrodes in the hippocampal CA1 to investigate pathophysiology in behaving rats post-TBI**.**

Disclosures: M. Habib: None. **C. Adam:** None. **E. Mirzakhalili:** None. **J.A. Wolf:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.16/VV63

Topic: H.08. Learning and Memory

Support: NSERC DG

Title: Activation of cell assemblies associated with rat's skilled reaching task is modulated by hippocampal sharp-wave ripples during sleep

Authors: P. NAZARI ROBATI, M. ECKERT, ***M. TATSUNO**;
Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Recent research suggests that explicit and implicit memories are represented by groups of anatomically or functionally connected neurons, called cell assemblies (CAs). For CAs associated with explicit memory, it has been reported that the hippocampal and cortical reactivation is coordinated during slow-wave sleep (SWS). However, our current understanding of the relationship between CAs associated with implicit memory and hippocampal activity remains limited. To address this gap, we analyzed neural ensemble activity in the primary motor cortex (M1) during behavioral task and rest periods in four rats that underwent training in a skilled single-pellet reaching task for approximately 15 days (Eckert et al., 2020). Based on the behavioral performance assessed by the success reach rate, four rats were categorized into two fast-learners and two gradual-learners. We applied an unsupervised CA detection method (Russo and Durstewitz, 2017) to the combined task and sleep recording and identified the CAs associated with reaching behavior. The K-means clustering on those reach-associated CAs

revealed that there were four distinct neural dynamics around the reach behavior. Reactivation analysis detected a significant increase of reactivation during post-task SWS than pre-task SWS (paired t-test, p-value< 0.05). Investigation of the hippocampal sharp-wave ripples (SWRs) and the reach-associated CAs revealed the presence of both positive and negative modulation of CAs around SWRs. To further investigate whether the CA modulation around SWRs is influenced by training, we compared the early and late training days. Interestingly, during the early phase of training, fast-learners exhibited more CA suppression around SWRs whereas the gradual learners showed more CA activation around SWRs (Mann-Whitney U test, p-value< 0.05). In conclusion, we found that reach-related CA reactivation in M1 could either be activated or suppressed around SWRs during sleep and that this relationship was different for fast and gradual learners. Our results suggest that cortical reactivation is coordinated with the hippocampus during skill learning and that a potential variation in underlying motor memory consolidation mechanisms leads to faster or slower learning.

Disclosures: **P. Nazari Robati:** None. **M. Eckert:** None. **M. Tatsuno:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.17/VV64

Topic: H.08. Learning and Memory

Support: F31MH134582

Title: Anterior cingulate cortex preferentially drives dorsal CA1 deep neuronal activity during sharp-wave ripples for memory consolidation

Authors: *A. HALL, D. V. WANG;
Drexel Univ. Col. of Med. Neurosci. Program, Philadelphia, PA

Abstract: Memories of events are committed to long-term storage through a process known as system consolidation. Sharp-wave ripples (SPWs), neural oscillations originating from hippocampal dorsal CA1 and occurring predominantly during slow-wave sleep (SWS), play a critical role in system consolidation. SPWs are thought to coordinate the reactivation of hippocampal and cortical ensembles (neural units that encode memories) that were previously active during wakeful memory acquisition. Recently, two subpopulations of hippocampal dorsal CA1 (dCA1) pyramidal neurons that exhibit unique firing properties during SPWs have been identified. Neurons in the superficial pyramidal layer of dCA1 (CA1sup) exhibit more rigid characteristics and show non-significant changes in activity in response to learning, whereas those in the deep pyramidal layer of dCA1 (CA1deep) exhibit more plastic-like characteristics, changing dynamically in response to learning. Although these functional differences have been described, the neural inputs which drive the recruitment of these neurons during SPWs, remains understudied. Evidence we have gathered suggests the anterior cingulate cortex (ACC) is a

possible candidate that drives dCA1 neuron recruitment during SPWs. Using viral labelling and dual site *in vivo* electrophysiology, we have traced a polysynaptic pathway connecting ACC to dCA1 and uncovered preliminary evidence demonstrating functional connectivity between these two regions. Specifically, we found that ACC neuronal population activity immediately preceding SPW onset predicts the firing rates of CA1deep but not CA1sup neurons during subsequent SPWs. Moreover, the predictive strength significantly increases in post-learning compared to pre-learning sleep, suggesting a likely role in memory consolidation. Consistently, optogenetic stimulation of the ACC during SWS selectively activates CA1deep but not CA1sup neurons. Given these findings, we hypothesize that ACC neurons selectively drive CA1deep, but not CA1sup neurons activity during SPWs of SWS, and that this communication is involved in the consolidation of newly acquired memories.

Disclosures: **A. Hall:** None. **D.V. Wang:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.18/WW1

Topic: H.08. Learning and Memory

Title: Closed-loop theta stimulation in the human hippocampus modulates sharp-wave ripple activity

Authors: *A. MISHRA[1], S. AKKOL[2], J. L. HERRERO[4], G. TOSTAEVA[5], E. ESPINAL[3], A. D. MEHTA[6], S. BICKEL[7];
[1]Zucker Sch. of Med. at Hofstra/Northwell, Hempstead, NY; [2]Feinstein Inst. for Med. Res., Manhasset, NY; [3]Feinstein Inst. for Med. Res., Philadelphia, PA; [4]Neurosurg., The Feinstein Inst. For Med. Res., Manhasset, NY; [5]The Feinstein Inst. for Med. Res., Manhasset, NY; [6]Neurosurg., Hofstra North Shore LIJ Sch. of Med., Great Neck, NY; [7]Neurosurg. - Neurol., Feinstein Inst., Manhasset, NY

Abstract: Neurological conditions impacting human memory represent a massive hurdle for modern medicine, and the investigation of neuroprosthetic devices that can interact with memory neurocircuitry via electrical stimulation is warranted. Hippocampal sharp-wave ripples (SWR) and hippocampal-neocortical theta oscillations are electrophysiological signatures of memory that coordinate memory storage and retrieval in memory networks. However, few studies have investigated direct causal relationships between theta oscillations and hippocampal SWR. In three patients, closed-loop stimulation was applied in theta frequency (10 pulses per stimulation train) directly to the hippocampus or to white matter tracts in the hippocampal-entorhinal region in- and out-of-phase relative to ongoing hippocampal theta oscillations. The selected stimulation frequency was subject-specific, as stimulation was applied with respect to each patient's resting peak hippocampal theta frequency. SWR characteristics and hippocampal theta power were evaluated both within the stimulation train and proceeding the end of stimulation. Relative to

baseline, in-phase theta stimulation (total 240 stimulation trials) evoked an increase in SWR rate that outlasted the end of stimulation train by 1.5 seconds. Across patients, stimulation-evoked SWR rate was 30% higher than baseline. Further, in trials with increased pre-stimulation hippocampal theta power, post-stimulation SWR rate was also elevated. This study corroborates a relationship between direct electrical stimulation and modulation of human memory neurocircuitry. The application of subject-specific electrical stimulation may evoke enhanced stimulation effect. The implementation of electrical stimulation to augment human memory is a promising frontier, and one that warrants further investigation.

Disclosures: **A. Mishra:** None. **S. Akkol:** None. **J.L. Herrero:** None. **G. Tostaeva:** None. **E. Espinal:** None. **A.D. Mehta:** None. **S. Bickel:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.19/WW2

Topic: H.08. Learning and Memory

Support: R01MH131559

Title: Transition from Rule- to Memory-based Strategy During Task Learning

Authors: *G. YANG, J. JIANG;
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Abstract: Different strategies can be utilized when performing tasks. It is usually the best to follow the rules (rule-based strategies) when tackling a task for the first time. However, with extensive practice, more efficient shortcuts (memory-based strategies) can be employed to reduce effort. For example, in the game Minesweeper, remembering how different patterns of numbers correspond to locations of mines can greatly improve performance. However, how practice leads to the switch from rule-based to memory-based strategies remains underexplored. This study aims to investigate the dynamics of applying different strategies in a sequence inference task. We designed a series of tasks, in which participants were initially trained to memorize two distinct task sequences (A and B, each with its unique order). They were then required to recall the task at specific positions of a sequence based on a given cue (e.g., fourth task of sequence A). We hypothesized that participants would start with rule-based strategy initially by mentally replaying the sequence from the beginning to the cued position, but would later switch to a memory retrieval strategy once they had learned the associations between the cues and responses. A total of 34 participants (24.6 ± 6.8 years old; 23 females) took part in the study. The behavioral results revealed that reaction was slower when cued for later positions, but this effect diminished as time progressed. To elucidate their behavioral performance, we developed a computational model that encompassed both the replay of task sequences and the reinforcement learning of associations. Consistent with our hypothesis, the modeling results

suggested that participants employed a replay strategy in the early stage, but transitioned to a memory retrieval strategy later and maintained it until the end. fMRI data during the sequence inference task showed that the replay process was encoded in the frontal-parietal and hippocampus regions. Moreover, the encoding gradually decreased over time, reflecting the shift towards the memory retrieval strategy. In conclusion, our findings demonstrate that sequential task events can be flexibly encoded in our memory, and how they are retrieved depends on the trade-offs between alternative strategies.

Disclosures: G. Yang: None. **J. Jiang:** None.

Poster

PSTR303. Hippocampal–Cortical Interactions II

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR303.20/WW3

Topic: H.08. Learning and Memory

Support: APP1091593
APP1117724
DP170101815

Title: Parcellation of the human hippocampus using track weighted dynamic functional connectivity: New insights into structure function relationships.

Authors: *M. A. DALTON, J. LV, A. D'SOUZA, F. CALAMANTE;
Univ. of Sydney, Sydney, Australia

Abstract: Recent technical and methodological advances allow us to conduct increasingly detailed investigations of structural connectivity (SC) and functional connectivity (FC) of the human hippocampus in-vivo using MRI. However, SC and FC are most often analysed independently, thereby limiting our ability to understand structure-function relationships of cortico-hippocampal connectivity in the human brain. To address this gap, we investigated the relationship between SC and FC of the human hippocampus using track-weighted dynamic functional connectivity (TW-dFC) mapping.
In brief, we fused SC and FC data into a quantitative 4D image (i.e., with spatial+temporal information) using TW-dFC. First, ten subjects were selected from the Human Connectome Project (HCP) 100 unrelated subject database. For each subject, we used DWI data to generate SIFT2 weighted streamlines and isolate those connecting the hippocampus with the rest of the brain ('hippocampus tractogram'). We calculated the TW-dFC map for the hippocampus tractogram by assigning each streamline a 'dynamic functional weighting' given by the functional correlation between resting state BOLD fMRI data at its end-points. The TW-dFC data were further analysed using independent component analysis (ICA) to identify clusters within the hippocampus based on the time-series associated with each hippocampal endpoint in the TW-dFC maps. This allowed us to characterise spatially distinct functional clusters within

the hippocampus in a data-driven manner. We then identified the distinct cortical networks associated with each functional cluster in a separate group of 100 participants using HCP data. Using this approach, we identified multiple spatially distinct functional clusters along both the anterior-posterior and medial-lateral axes of the human hippocampus. Group level analysis confirmed that separate functional clusters within the hippocampus were associated with distinct cortical networks, each associated with their own dynamic functional fingerprint. For example, we found strong functional associations between the posterior medial hippocampus and specific medial parietal/occipital areas and, in contrast, between the anterior lateral hippocampus and temporal brain areas.
Our results revealed how circumscribed regions within the human hippocampus display anatomical and dynamic functional connectivity with distinct cortical areas and provide new detailed insights into structure-function relationships within the human hippocampus. These results have implications for theories of human hippocampal function and for understanding hippocampal (dys)function in health and disease.

Disclosures: **M.A. Dalton:** None. **J. Lv:** None. **A. D'Souza:** None. **F. Calamante:** None.

Poster

PSTR304. Intrinsic Hippocampal Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR304.01/WW4

Topic: H.08. Learning and Memory

Support: JSPS KAKENHI for Early-Career Scientists (22K15209)
JSPS KAKENHI (JP18H05432)
Brain/MINDS from AMED (JP19dm0207001)
Miller Institute for Basic Research in Science
Burroughs Wellcome Fund Collaborative Research Travel Grant

Title: Distinguishing examples while building concepts in hippocampal and artificial networks

Authors: *L. KANG, T. TOYOIZUMI;
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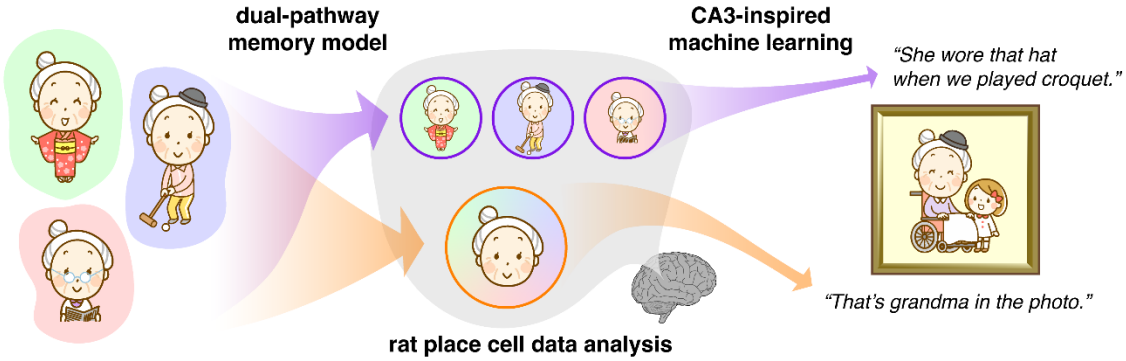
Abstract: The hippocampal subfield CA3 is thought to function as an autoassociative network that stores experiences as memories. Information from these experiences arrives via the entorhinal cortex (EC), which projects to CA3 directly as well as indirectly through the dentate gyrus (DG). DG sparsifies and decorrelates the information before also projecting to CA3. The computational purpose for receiving two encodings of the same sensory information has not been firmly established. We model CA3 as a Hopfield-like network that stores both correlated and decorrelated encodings and retrieves them at low and high inhibitory tone, respectively. As more memories are stored, the dense, correlated encodings merge along shared features while the sparse, decorrelated encodings remain distinct. In this way, the model learns to transition

between concept and example representations by controlling inhibitory tone. To experimentally test for the presence of these complementary encodings, we analyze the theta-modulated tuning of place cells in rat CA3. In accordance with our model's prediction, these neurons exhibit more precise spatial tuning and encode more detailed task features during theta phases with sparser activity. Finally, we generalize the model beyond hippocampal architecture and find that feedforward neural networks trained in multitask learning benefit from a novel loss term that promotes hybrid encoding using correlated and decorrelated representations. Thus, the complementary encodings that we have found in CA3 can provide broad computational advantages for solving complex tasks.



Disclosures: **L. Kang:** None. **T. Toyoizumi:** None.

Poster

PSTR304. Intrinsic Hippocampal Circuits

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR304.02/WW5

Topic: H.08. Learning and Memory

Support: CRCNS R01

Title: Unsupervised hippocampal replay evaluation based on extended Poisson Gaussian-Process Latent Variable Model

Authors: ***D. D. LUO**[1], B. GIRI[2], K. DIBA[3], C. KEMERE[4];
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Abstract: It has been shown that the hippocampus plays a major role in memory and its activity is tuned by a wide variety of variables. Hippocampal neural firing patterns during behavior are found to be replayed in a temporally-compressed manner during those population burst events (PBEs) that occur during sharp-wave ripple oscillations, which is thought to be important for

memory consolidation. However, our understanding of those replay events is biased because of the many assumptions imposed in replay detection. To decode and detect replay events in an unsupervised manner, dimension reduction on neural activity paves a way for it by dissociating the measurement of internal neural state repetition from the measurement of external variable tuning.
With assumptions only on the smoothness of latent dynamics and of internal tuning curves, the Poisson Gaussian-process latent variable model (P-GPLVM) (Wu et al., 2017) is a powerful tool to discover the low-dimensional latent structure for high-dimensional spike trains. We extend the P-GPLVM to enable the latent variable inference of new data constrained by the previously learned smoothness and mapping information, thereby allowing the estimation of internal state repetition in new neural activity. We also describe a principled approach for the constrained latent variable inference for temporally-compressed patterns of activity, such as those found in PBEs, as well as metrics for assessing neural state repetition and repetition pattern, which allows replay detection without assuming external variables that drive the neural activity or predetermining replay patterns.
These approaches are applied on hippocampal ensemble neural activity recorded in an experiment where the animal explored two mazes and rested before and after both exploration sessions. A latent space encoding animal position and context is learned merely from neural activity during active maze explorations. Tested by new neural data during active exploration, this extended P-GPLVM can capture the repetition of neural states encoding similar animal experiences. Likewise, neural state repetitions can be evaluated for neural activity during PBEs, allowing the unsupervised identification for replay events of versatile replay patterns and more general experiences.

Disclosures: **D.D. Luo:** None. **B. Giri:** None. **K. Diba:** None. **C. Kemere:** None.

Poster

PSTR304. Intrinsic Hippocampal Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR304.03/WW6

Topic: H.08. Learning and Memory

Support: NIH F30 MH126607
NIH U01 NS122124

Title: Hippocampal contributions to dynamic social memory in prairie voles.

Authors: *W. M. SHEERAN[1,4,2], K. E. WINTHER[2], J. A. TEMPLE[3], Z. R. DONALDSON[2,3]; [2]Molecular, Cellular, and Developmental Biol., [3]Psychology and Neurosci., [1]Univ. of Colorado, Boulder, CO; [4]Med. Scientist Training Program, Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Substantial work over the past decade has implicated the dorsal CA2 (dCA2)-to-ventral CA1 (vCA1) intrahippocampal circuit in processing social information and related

memories. In mice, activity in both regions is necessary for hours-to-days-long social recognition memory. Both regions also contain neuronal ensembles whose activity discriminates between different conspecific identities. However, several critical questions about this circuit's role in social information processing remain unanswered. For example, how do neuronal dynamics in either region compare as a test animal recognizes conspecifics with fundamentally distinct relationships to itself, such as a peer or a mating partner? Additionally, how stable is coding for a conspecific if the test animal successfully remembers that individual after a long period of separation? Answering these questions requires an animal model that forms multiple distinct attachment relationships and exhibits long-term social memory. Unlike laboratory mice and rats, prairie voles develop same sex affiliative relationships and opposite-sex pair bonds and remember these relationships even after weeks of separation. Using in vivo cellular resolution calcium imaging and manipulative methods in dCA2 and vCA1, our preliminary results indicate that vCA1 is required for prairie voles to form new pair bonds. Additionally, distinct ensembles discriminating a partner from a novel animal exist in dCA2 before and after partner separation. We are continuing to record activity from and are planning to reversibly inhibit both regions throughout the time course of peer relationships and pair bonds.

Disclosures: W.M. Sheeran: None. **K.E. Winther:** None. **J.A. Temple:** None. **Z.R. Donaldson:** None.

Poster

PSTR304. Intrinsic Hippocampal Circuits

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Program #/Poster #: PSTR304.04/WW7

Topic: H.08. Learning and Memory

Support: JSPS KAKENHI Early Career Investigator Grant

Title: Bidirectional impact on memory formation by local dendrite-targeting CA1 hippocampal interneurons

Authors: *V. SEKULIC, Y. LIU, D. POLYGALOV, A. HUANG, T. J. MCHUGH;
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Abstract: In mammals, the formation of new memories critically depends on the balance of excitation and inhibition within the circuits of the hippocampus, controlled by a large array of distinct interneuron subtypes. In the CA1 region, somatostatin-expressing (SST) interneurons target pyramidal cell dendrites and *in vitro* these SST+ cells have been shown to simultaneously inhibit distal dendrites but disinhibit proximal dendrites in CA1 pyramidal neurons, suggesting a complex role in modulating principal cell activity during memory encoding. We thus sought to determine the effects of bidirectional SST cell manipulation on hippocampal learning *in vivo* using a combination of chemogenic manipulation (DREADDs) and genetically encoded calcium indicator activity (Soma.GCaMP6f) as readouts in freely behaving mice. We observed that

DREADD-mediated activation of SST+ neurons during training in the trace fear conditioning (TFC) task resulted in enhanced memory 1 week later and an increase in the size of the CA1 engram, while SST+ neuron inhibition decreased both memory and engram size. Calcium imaging analysis found that pyramidal cells exhibited higher firing rates, greater number of place fields, and less spatially selective fields in the SST activation compared to inhibition and mCherry control groups, suggesting a more generalized encoding of memory during TFC. Conversely, the SST inhibition group exhibited more spatially selective, and thus less out-of-field activity than both the activation and control groups. This led us to the prediction that spatial coding may be enhanced in SST inhibition mice compared to SST activation, which was subsequently confirmed in an object location task (OLT) experiment. Our findings suggest a role for SST interneurons *in vivo* that combines both inhibitory and disinhibitory effects depending on whether the memory type is mediated by contextual (proximal) or sensory (distal) information onto CA1 pyramidal dendrites.

Disclosures: **V. Sekulic:** None. **Y. Liu:** None. **D. Polygalov:** None. **A. Huang:** None. **T.J. McHugh:** None.

Poster

PSTR304. Intrinsic Hippocampal Circuits

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR304.05/WW8

Topic: H.08. Learning and Memory

Support: NSERC CRSNG

Title: Disruption of mTORC1-4EBP2 signaling in inhibitory but not excitatory neurons promotes hippocampal-dependent learning and memory impairment

Authors: S. WIEBE[1], ***Z. HUANG**[2], A. NAGPAL[1], C. WALTERS[4], N. MAHMOOD[3], J.-C. LACAILLE[5], N. SONENBERG[1,6];
[1]McGill Univ., [2]Biochem., McGill Univ., Montreal, QC, Canada; [3]Niaz Mahmood, McGill Univ., MONTRÉAL, QC, Canada; [4]McGill Univ. Integrated Program in Neurosci., McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada; [5]Univ. De Montreal, Univ. De Montreal, Montreal, QC, Canada; [6]Rosalind and Morris Goodman Cancer Inst., Montreal, QC, Canada

Abstract: Memory disorders are associated with Alzheimer's disease, traumatic brain injuries, and aging. Understanding the molecular mechanisms underlying memory formation, storage, and retrieval is cardinal to finding new treatments. Protein synthesis plays a crucial role in memory formation by enabling enduring forms of synaptic plasticity. The mechanistic target of rapamycin complex 1 (mTORC1) contains the regulator-associated protein of mTOR (Raptor) and phosphorylates eukaryotic initiation factor (eIF) 4E-binding proteins (4E-BPs). Phosphorylated 4E-BPs dissociate from the cap-binding protein eIF4E, which then bind to the

mRNA and initiate protein synthesis. We discovered that hippocampal mTORC1 activity sharply declines in the excitatory pyramidal neurons during postnatal development in mice but maintains at a high level in GABAergic neurons. We employed a combination of genetic and chemogenetic methods to study the cell-type-specific role of the mTORC1-4EBPs axis in learning and memory. Our results demonstrate that deleting Raptor or 4E-BP2 (the major brain isoform) in GABA-expressing inhibitory neurons is sufficient to cause hippocampal-dependent memory impairment. Both exaggerating and attenuating mTORC1 activity using DREADDS in hippocampus inhibitory neurons, but not excitatory neurons, blocks long-term memory formation. Taken together, our research highlights the importance of mTORC1-4EBP2 activity in GABAergic inhibitory neurons in learning and memory.

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Poster

PSTR304. Intrinsic Hippocampal Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR304.06/WW9

Topic: H.08. Learning and Memory

Support: NIH Grant GM118801

Title: Both interneuronal and pyramidal cell α5-GABA$_a$receptors modulate the threshold of LTP induction

Authors: *S. KOMANDURI[1], M. N. DREGER[1], R. A. PEARCE[2];
[1]Dept. of Anesthesiol., Univ. of Wisconsin - Madison Sch. of Med. and Publ. Hlth., Madison, WI; [2]Dept. of Anesthesiol., Univ. of Wisconsin-Madison Sch. of Med. and Publ. Hlth., Madison, WI

Abstract: GABAA receptors that incorporate α5-subunits (α5-GABA$_A$Rs) are expressed throughout the central nervous system, but they are most highly concentrated within the hippocampus, a structure that plays an essential role in learning and memory. To investigate the mechanisms by which α5-GABA$_A$Rs modulate memory, we selectively eliminated them from pyramidal neurons or interneurons and assessed effects on long-term potentiation (LTP) of Schaffer Collateral (SC) synapses in hippocampal brain slices, a commonly used cellular model of memory formation. Stimulus and recording electrodes were placed in *stratum radiatum*, and LTP was induced by a tetanic stimulus consisting of 600 pulses delivered at a frequency of 20Hz, a paradigm that was reported previously to depend upon α5-GABA$_A$Rs (LJ Martin et al., J. Neurosci. 2010). LTP was quantified as the change in the average fEPSP slope between 50-60 min post-tetanus. Differences were compared using one-way ANOVA and Tukey's HSD test to correct for multiple comparisons, with statistical significance set at p=0.05. We found that LTP was significantly greater in global α5-subunit knockout mice compared to WT (α5-gl-KO 19.6 ±

8.0%, WT -3.90± 15.1%, p=0.007, n=8 each), confirming previous results. In mice lacking α5-GABAARs in either interneurons or pyramidal neurons, LTP was also significantly greater than WT (α5-i-KO 33.14 ± 10.1%, p=0.0042; α5-pyr-KO 26.81 ± 17.9%, p=0.00003, n=8 each). There were no statistically significant differences between the α5-gl-KO, α5-i-KO, and α5-pyr-KO groups. Our results indicate that α5-GABA$_A$Rs on both interneurons and pyramidal cells set the threshold for LTP in this 20Hz tetanus paradigm. Future studies of interneuron subtype-selective a5-GABA$_A$R knockout mice will reveal which interneuron subtypes are involved.

Disclosures: S. Komanduri: None. **M.N. Dreger:** None. **R.A. Pearce:** None.

Poster

PSTR304. Intrinsic Hippocampal Circuits

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Topic: H.08. Learning and Memory

Support: MEXT/JSPS KAKENHI JP20H05053
MEXT/JSPS KAKENHI JP21H05242
MEXT/JSPS KAKENHI JP19H03342
AMED Brain/MINDS JP19dm0207089
JST CREST JPMJCR1751 JST SPRING
Takeda Science Foundation

Title: Decreased hippocampal CA1 sharp-wave ripples during consummatory reward licking in head-fixed rats

Authors: *T. SAKAIRI[1], M. KAWABATA[1], A. RÍOS[1], Y. SAKAI[2], Y. ISOMURA[1];
[1]Tokyo Med. and Dent. Univ., Tokyo, Japan; [2]Tamagawa Univ. Brain Inst., Tokyo, Japan

Abstract: In psychology, animals are sometimes considered to behave in a sequence of actions consisting of approaching a desire (preparatory/appetitive behavior) and finally satisfying the desire (consummatory behavior). Preparatory behaviors are exploratory and strategic for accomplishing their desire, whereas consummatory behaviors include drinking, eating, and copulating for consummation (Konorski, 1976). It is known that sharp-wave ripples (SWRs) occur in the hippocampus during consummatory behaviors as well as awake immobility and slow-wave sleep (Buzsaki, 1986). For instance, the SWRs are increased when animals acquire a reward (i.e., consummatory behavior) after they explore space in expectation of reward (preparatory behavior). These SWRs may take a role in memory consolidation on exploratory action and its outcome. However, it remains unclear whether immobility or consummation contributes more to modulating the occurrence of SWRs, since they stand still to get the reward under such freely-moving conditions. To address this issue, we analyzed the SWRs and spike activity in the hippocampal CA1 area during licking a drop of water in constantly immobile rats under a head-fixed condition. We preliminarily observed the SWRs significantly decreased when

naïve (unlearned) rats licked to drink water under the constant immobility. Therefore, we investigated whether this unexpected decrease in SWRs would also be reproduced during licking reward water as a consummatory behavior in an operant learning task. To this end, we trained head-fixed rats to perform a "False-True Consummation" task, in which each pedal release in response to go cue (preparatory action) was unrewarded and rewarded alternately. Thereby, their licking was considered as false and true consummation in unrewarded and rewarded trials, respectively. We found that the SWRs gradually significantly increased towards the pedal release (preparatory action) especially in reward-expectable trials. Intriguingly, the SWRs were rapidly suppressed during true consummatory licking in rewarded trials under the immobility. In addition, a group of hippocampal CA1 neurons displayed a similar decrease in spike activity during the consummatory licking. These results indicate that reward expectation enhances the SWRs occurrence during preparatory behavior and that it was notably suppressed during the consummatory action in constantly immobile situation.

Disclosures: **T. Sakairi:** None. **M. Kawabata:** None. **A. Ríos:** None. **Y. Sakai:** None. **Y. Isomura:** None.

Poster

PSTR304. Intrinsic Hippocampal Circuits

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Program #/Poster #: PSTR304.08/WW11

Topic: H.08. Learning and Memory

Support: CIHR

Title: The Effects of Silencing Dorsal and Ventral Hippocampus in a Probabilistic Reversal Learning Task in Rats

Authors: *M. COOKE, T. LIN, B. DUNGATE, P. HOLDER, S.-A. CHOI, L. MALLELA, J. SCHUMACHER, S. FLORESCO, J. SNYDER;
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Abstract: In nature, animals searching for reward, whether food or otherwise, are often not guaranteed success. Animals, and humans, must therefore learn and adapt to these uncertainties and flexibly update their cognitive representations of where and how to procure rewards. This cognitive flexibility is disrupted in psychiatric disorders such as depression, OCD, schizophrenia, and many others. Structurally, these probabilistic outcome associations have been associated mainly with the orbitofrontal cortex, striatum, and amygdala. However, previous work in our lab has shown that the disruption of hippocampal neurogenesis alters reward feedback sensitivity. We therefore hypothesized that the hippocampus, with its projections to cortical regions, amygdala and striatum, may play a critical and understudied role in probabilistic learning. However, the hippocampus is a large and complex structure. Hippocampal function has often been divided into dorsal and ventral aspects; the dorsal hippocampus performing primarily

cognitive functions such as spatial navigation and the ventral encoding emotional valence. Although classically dichotomised, recent research has shown that both the dorsal and ventral hippocampus are involved in many aspects of learning and memory. Our goal with this work is therefore twofold: provide evidence that the hippocampus plays a role in probabilistic learning, and determine which areas of the hippocampus are recruited. In our probabilistic reversal learning task, rats must learn to differentiate between a lever that rewards 80% of the time and one that rewards 20% of the time in an operant chamber. Once the animal has successfully identified and responded on the correct (80%) lever 8 consecutive times, the reward contingencies switch. We have run a successful group of 8 male and 8 female rats through this paradigm and inactivated the dorsal hippocampus using DREADDs. We observed a significant difference in the number of lever reversals between inactivated and control groups, but only in female rats. We are in the process of replicating the dorsal inactivation, as well as inactivating the ventral hippocampus in separate cohorts of rats. Through this work we hope to better understand the physiology of these behaviours, and provide insight into potential therapeutic interventions for various psychiatric disorders.

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Poster

PSTR304. Intrinsic Hippocampal Circuits

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Topic: H.08. Learning and Memory

Support: Whitehall Foundation Grant 2017-08-31 (to Uwe Rudolph)
College of Veterinary Medicine, UIUC, Startup Fund (to Uwe Rudolph)

Title: Modulation of Anxiety and Fear via Distinct Intrahippocampal Projections to Ventral CA1

Authors: *M. KAMBALI[1], M. WANG[1,2], R. NAGARAJAN[1], J. LYU[1,2], H. GRITTON[1], U. RUDOLPH[1];
[1]Dept. of Comparative Biosci., Univ. of Illinois, Urbana-Champaign, Urbana, IL; [2]Neurosci. Program, Univ. of Illinois, Urbana-Champaign, Urbana, IL

Abstract: Anxiety and fear are distinct emotional states triggered by different factors. Increased anxiety arises from the anticipation of potential threats, resulting in heightened alertness, while fear is evoked by harmful stimuli, leading to defensive or retreat behaviors. The ventral hippocampus is known to be involved in the modulation of anxiety- and fear-related behaviors. Previously, we showed that inhibiting dentate gyrus and CA3 principal neurons through α2-containing $GABA_A$ receptors (α2-$GABA_A$Rs) is necessary for the reduction of anxiety by diazepam, whereas inhibition of CA1 pyramidal neurons via α2-$GABA_A$Rs is necessary for diazepam-induced suppression of fear responses. In this study, we wanted to test the hypothesis

that while the CA3 to CA1 projection would modulate anxiety-related behavior, the direct projection from EC to CA1 would modulate fear-related behavior. To test this hypothesis, we used optogenetics to modulate ventral intrahippocampal projections bidirectionally. Adult C57BL/6J mice were subjected to bilateral stereotaxic injection of a viral vector expressing channelrhodopsin or halorhodopsion [AAV-CamKIIa-hChR2(H134R)-EYFP or AAV-CamKIIa-eNpHR3.0-EYFP or AAV-CamKIIa-EYFP] into vCA3 or into layers II-III of entorhinal cortex, followed by bilateral implantation of fiberoptic ferrules into vCA1. After three weeks of recovery, mice were assessed for anxiety-like behavior in the open field and the elevated plus maze, followed by the Vogel conflict test, and by contextual and trace fear conditioning for fear assessment. The behavior of the mice was recorded under laser 'ON' and 'OFF' conditions in all experiments. Activation of the vCA3 to vCA1 projection with a blue laser (473 nm, activating channelrhodopsin) decreased anxiety- and increased fear-related behavior, while inhibition of this projection with a yellow laser (593.5 nm, activating halorhodopsin) increased anxiety- and decreased fear-related behavior. Optogenetic activation or inhibition of the EC to vCA1 projection did not affect anxiety-related behavior. In contrast, optogenetic activation of the EC to vCA1 projection increased, and optogenetic inhibition of the EC to vCA1 projection decreased fear-related behavior. These results suggest that vCA3 pyramidal projections to vCA1, but not the EC projections to vCA1, modulate anxiety-like behavior, while both vCA3 to vCA1 projections and entorhinal cortical projections to vCA1 play a role in modulating fear responses. Thus, while fear-related behavior is modulated by both inputs to vCA1, modulation of anxiety-related behavior is input-specific for the vCA3 to vCA1 projection.

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Poster

PSTR304. Intrinsic Hippocampal Circuits

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Program #/Poster #: PSTR304.10/WW13

Topic: H.08. Learning and Memory

Support: Alzheimer Society of Canada Proof of Concept Grant
CFI Leaders Opportunity Fund

Title: Firing rate modulation by sharp wave ripples of dorsal CA1 excitatory neurons is decoupled from environmental novelty in the TgCRND8 mouse model of Alzheimer's disease

Authors: *Y. SUN[1,2], S. CHEKHOV[3], S. MARGARIAN[3], D. ZHAO[3], P. E. FRASER[4,5], K. TAKEHARA-NISHIUCHI[1,2,3];
[1]Cell and Systems Biol., [2]Collaborative program in Neurosci., [3]Psychology, [4]Tanz Ctr. for Res. in Neurodegenerative Dis., [5]Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada

Abstract: Alzheimer's disease (AD) is a progressive neurological disease associated with the decline in episodic memory. Critical for memory consolidation, sharp wave ripples (SWR) are transient bursts of oscillatory activity (150-250 Hz) in the hippocampus that occur during slow wave sleep and awake rest. Although abnormal SWRs parallel memory deficits in several mouse models of AD, the corresponding deficits of single neuron activity supporting memory and learning remain unknown. We used an array of wire electrodes to record neuronal activity from the dorsal hippocampal CA1 of 3-5 month-old wildtype (WT) and TgCRND8 mice with AD-related amyloidosis and spatial memory deficits. Recordings were performed over two days during rest before (PRE) and after (POST) two types of awake experience: 1) exploration of a familiar environment and 2) exploration of novel objects in a familiar environment. From the recorded signals, the spiking activity of individual neurons was isolated and further classified into putative pyramidal neurons and interneurons based on spike waveforms and temporal patterns. During the PRE sessions, firing rates of putative interneurons within and outside SWR events were significantly lower in TgCRND8 mice than WT mice, while firing rates of putative pyramidal neurons were lower only during SWRs. Both neuron subtypes increased their firing rates during SWRs relative to baseline, however this SWR modulation of firing rates was weakened in TgCRND8 pyramidal neurons. Furthermore, firing rates of WT pyramidal neurons during SWRs were increased in POST compared to PRE sessions after familiar and novel experiences, whereas firing rates outside SWRs were unchanged. As a result, the degree of SWR modulation was strengthened after both experiences. In contrast, pyramidal neurons in TgCRND8 mice showed increased firing rates during SWRs in POST sessions after the familiar but not novel experience. These neurons also increased their firing rates outside SWRs after both experiences. Due to this non-specific firing rate increase, experience-induced strengthening of SWR modulation was absent in TgCRND8 pyramidal neurons. None of these experience-dependent changes in firing rates were detected in putative interneurons in either genotype. Our observations suggest that early-stage amyloidosis differentially affects spiking dynamics of hippocampal pyramidal neurons and interneurons during SWRs, and the lack of proper activity restructuring in response to environmental novelty may be a mechanism underlying associated memory deficits.

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Poster

PSTR304. Intrinsic Hippocampal Circuits

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Support: European Research Council grant 647954
European Research Council grant 715714
Wellcome Trust/Royal Society Sir Henry Dale Fellowship (107672/Z/15/Z)

Title: Hippocampal neurons code individual episodic memories in humans

Authors: *L. D. KOLIBIUS[1], F. ROUX[2], G. PARISH[3], M. TER WAL[4], M. VAN DER PLAS[5], R. CHELVARAJAH[6], V. SAWLANI[7], D. ROLLINGS[7], J. LANG[8], S. GOLLWITZER[8], K. WALTHER[8], R. HOPFENGÄRTNER[8], G. KREISELMEYER[9], H. HAMER[9], B. STARESINA[10], M. WIMBER[11], H. BOWMAN[12], S. HANSLMAYR[11];
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Abstract: The hippocampus is an essential hub for episodic memory processing. Despite this, little is known about how neurons in the hippocampus encode and retrieve new episodes. Some argue that each hippocampal neuron codes for an invariant element within an episode. Instead, others have proposed that hippocampal neurons bind together all elements present in a discrete episodic memory. Here, we provide evidence for the latter.
We show that individual neurons, which we term Episode Specific Neurons (ESNs), code discrete episodic memories using either a rate code or a temporal firing code. We find evidence for these neurons exclusively in the hippocampus. Importantly, these ESNs do not reflect the coding of a particular element in the episode (i.e., concept or time). Instead, they code for the conjunction of the different elements that make up the episode.
Next, we will extend these findings to population activity in the local field potential. We report evidence for a reinstatement in high frequency power during successful memory processing that mirrors earlier findings in single neurons. Again, these results cannot be explained by activity induced by a content-code.
Lastly, we embed these findings in the broader literature, identify future experiments, and discuss possible translational applications.

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Poster

PSTR305. Learning and Memory: Oscillations

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Title: Eeg-tms revealing top-down cortical interactions underlying episodic memory

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Abstract: Integrating diverse elements into a cohesive memory representation is a hallmark of episodic memory formation and is believed to be guided by top-down executive control. Rhythmic fluctuations in the theta band (4-8 Hz) are thought to reflect such memory control processes, with the phase of prefrontal theta oscillations acting as a gate for recurrent cortical communication. However, the specific mechanisms underlying top-down interactions involved in memory formation remain elusive. We hypothesized that effective connectivity between the dorsomedial prefrontal cortex (DMPFC) and distant cortical regions involved in processing memory-related information is modulated by the frontal theta phase and supports episodic memory encoding. We utilized EEG to assess the propagation of neuronal activity from the DMPFC to downstream regions, resulting from TMS stimulation during an associative memory task. Single-pulses of TMS were delivered at random theta phases, either during task performance or rest periods. This design allowed us to investigate task-dependent and phase-dependent signal propagation dynamics. Importantly, by measuring memory performance, this design also enables the investigation of how signal propagation is associated with successful memory formation. We analyzed TMS-evoked potentials (TEPs) to track the directional propagation of brain activity from the DMPFC. Following TMS, a negative TEP emerged over the stimulated region at 10-50 msec post-TMS. This initial negativity subsequently spread to frontal-central sites at 100-120 msec post-TMS. At 150-190 msec post-TMS, a change in activation pattern occurred, manifested as positive activity at central electrodes. In order to examine the magnitude and spatial distribution of task-induced theta oscillations, EEG was recorded without TMS in a separate group of subjects who performed the same task. Utilizing guided source separation analysis, a distinct medial-prefrontal theta component centred around the Fz frontal electrode was isolated. The observed prefrontal theta oscillations and TEPs demonstrate the dynamic nature of cortical excitability during memory formation. These findings provide a foundation for further investigations into the causal role of top-down neuronal interactions in the process of episodic memory formation.

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Poster

PSTR305. Learning and Memory: Oscillations

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Program #/Poster #: PSTR305.02/WW16

Topic: H.08. Learning and Memory

Title: The Neurobiology of False and True Memory: Examination with EEG Oscillations

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Abstract: Memory errors, or false memories, are obscure cognitive processes that can result from bias, stereotypes, or expectations that influence our current thinking. These situations, which can be experienced by people of all ages, whether they have a neurological problem or not, cause conflicts in daily life. To make this situation more understandable, scientists have done research and used various paradigms to detect and measure memory errors and examine their conditions. The most well-known and outstanding of these is the DRM paradigm (Deese-Roediger-McDermott). However, various neuroimaging techniques have been used in the literature to learn how memory errors are activated in the brain. In particular, electroencephalography (EEG) is one of the most preferred neuroimaging methods by researchers as it provides a useful environment for the easy application of paradigms. In this study, brain waves will be examined by using EEG while memory errors are created with the DRM paradigm, and it will contribute to the literature by clarifying the neural network and its pattern, which is a marker that distinguishes false memory from true memory. Method: The study will be carried out in the Medipol University, Neuromodulation Laboratory with 30 participants who agreed to participate in the experiment and signed the consent form. Afterwards, a MoCA (Montreal Cognitive Assessment) test will be performed to measure cognitive skills and participants who get enough points will be included in the experiment. After the preparatory procedures for EEG recording, the participants will be taken to the EEG recording room. For the experiment design, 10-15 word lists created with E-prime software and adapted from the DRM paradigm will be projected onto the computer screen and the participants will be asked to try to memorize the words. After the memorization process is over, the previously presented new words, including the lure words, will be reflected on the screen, and the participants will be asked to answer the old or new words by pressing the keys determined on the keyboard, and memory errors will be measured and analyzed. Conclusion : With the analysis of EEG data, neural networks and brain activation patterns of information encoding, retention and correct or incorrect retrieval processes will be established and shed light on the literature on this subject.

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Poster

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Topic: H.08. Learning and Memory

Support: MH100820
MH127483

Title: Drastic changes in sleep spindle dynamics induced by activation of Cannabinoid-1 receptors

Authors: *I. TOPCHIY, B. KOCSIS;
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Abstract: Activation of cannabinoid-1 receptors (CB1-R) was shown to interfere with neuronal oscillations in cortical and hippocampal networks. Sleep spindles are unique among network oscillations, being generated by interplay of thalamic and thalamo-cortical networks. Both in the thalamus and in the cortex, they depend on fast firing parvalbumin interneurons and CB1-Rs were shown to be present at both thalamic and cortical sites. The goal of this study was to investigate sleep spindle dynamics following CB1-R activation in freely behaving rats. The rats were prepared for electrophysiological recordings over the frontal cortex and HPC along with neck muscle activity. Sleep was scored to identify waking and sleep stages, including rapid eye movement sleep (REMs), slow wave sleep (SWS), and intermediate sleep (IS) episodes. This latter is a short episode at the SWS-to-REMs transition when cortical spindles appear on the background of fully established REM sleep-like activity, i.e. theta rhythm in HPC and low-amplitude high-frequency activity in the cortex. Bouts of IS and REM sleep of the entire recording, including pre- and post- saline or CP-55,940 injections, were selected for analysis. Spectral analysis was performed using Fast Fourier Transform and the architecture of each spindle was analyzed using the matching pursuit algorithm. We found that following the injection of the CB1-agonist average length of IS episodes increased from 24.9±1.5 s, starting in the first hour post-injection to reach a maximum of 111.7±20.6 s by the 8th hour, The longest individual IS episodes (>80 s in all rats) were close to or even exceeding (>150 s in three rats) the average length of control REMs (147.1±14). Due to long IS, the rats spent over three times longer in the state of IS than before the injection, even though the frequency of IS episodes remained stable after drug injection. Total spindle-time also increased after CP-55,940 injection, due to progressive increase in the number of spindles generated in each IS episode ($p=0.001$; 7.9±0.7 pre- and 21.3±1.8 post-injection) and an increase in their length ($p=0.023$; 1.8±0.2s and 2.8±0.2s), whereas spindle density remained unchanged ($p=0.076$; 18.43±1.26 to 15.28±0.71). Spindle architecture also drastically changed. Post-injection, the centers of MP-atoms shifted from the normal 8-16 Hz frequency range to lower frequencies distributed in a narrower range below 10 Hz. Spindle activity was shown to play a role in memory consolidation and thus its alteration may be involved in the complex effect of CB1-R on cognition, including cognitive deficits in schizophrenia.

Disclosures: I. Topchiy: None. **B. Kocsis:** None.

Poster

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Topic: H.08. Learning and Memory

Title: Oscillatory signatures of arithmetic strategies in the left parietal cortex: a transcranial alternating current stimulation study

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Abstract: The strategies for solving arithmetic problems are typically inferred from the problem size and operation type. Solutions to simple (e.g., one-digit) and complex problems (e.g., double-digit) are assumed to be retrieved and calculated, respectively. Rote-learned multiplication is also thought to be solely solved by arithmetic fact retrieval, while subtraction is through procedural operations such as online counting. The neural underpinnings of arithmetic operations are embodied in the Triple Code Model (TCM) of number processing; for multiplication, verbal code in the left angular gyrus (AG) is used in the retrieval of arithmetic facts from long-term memory, while for subtraction, the magnitude code in bilateral intraparietal sulcus's horizontal segment (hIPS) is used for manipulating numerical quantities. However, studies using trial-by-trial questionnaires revealed that individuals use different strategies to solve one type of arithmetic operation. Nonetheless, oscillatory activities in the parietal cortex seem to index specific arithmetic strategies: higher left-hemispheric theta (4-7 Hz) event-related synchronization (ERS) is evoked by small problems and fact retrieval, while large problems and procedural strategies evoke alpha (8-12 Hz) event-related desynchronization (ERD). To test the causality of these findings, we applied transcranial alternating current stimulation (tACS) at individual participants' theta and alpha peak frequency to the left AG or hIPS concurrent with multiplication and subtraction tasks performance. The twenty participants answered a trial-by-trial questionnaire to indicate whether they retrieved or calculated the answers. The results showed that theta tACS over the left AG shortened RTs for multiplication and subtraction problems when answers were retrieved from memory. In contrast, left hIPS alpha tACS shortened RTs only for subtraction problems where the answers are calculated. This double-blinded study showed that theta oscillation at the left AG and alpha oscillation at the left IPS could be considered the neural signature of arithmetic fact retrieval and calculation procedure, respectively.

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Poster

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Program #/Poster #: PSTR305.05/WW19

Topic: H.08. Learning and Memory

Support: FRQNT Audace

Title: Modulating sleep spindles through auditory stimulation: a physiological perspective

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[1]Psychology, Concordia Univ., MONTREAL, QC, Canada; [2]Psychology, Concordia Univ., Montreal, QC, Canada

Abstract: Sleep spindles and slow oscillations are crucial for memory consolidation and can be enhanced or evoked through closed-loop auditory stimulation (CLAS) of slow oscillation up-states. As slow oscillations and sleep spindles may play different roles in memory consolidation (e.g., Cox et al., 2014, Nishida et al., 2007) and their relative timing may be a key factor in successful memory consolidation (Helfrich et al., 2018), it would be useful to have a means of causally manipulating sleep spindles non-invasively in healthy human subjects. However, CLAS of spindles is technically challenging due to their short duration (less than 3 s) and high frequency (11-16 Hz). Furthermore, previous research has suggested that sleep spindles may act to block sensory information passing through the thalamus, in which case, timing stimulation to coincide with spindles may be ineffective. To address these issues, we have developed a device, called the Portiloop, that detects and stimulates endogenous sleep spindles in real-time (Valenchon et al., 2022). In the present work, we conducted a pair of studies using the Portiloop for CLAS of spindles as well as stimulation that was randomly timed with respect to the phase and evolution of endogenously-generated sleep spindles. We evaluate whether sleep spindles can be manipulated with sound, and if so, how stimulation should be timed. In a first study (N = 40), we used the Portiloop to stimulate sleep spindles in a nap design, and report the physiological differences between stimulated and unstimulated sleep spindles. In a second (overnight) study (N = 20; 5 consecutively-recorded nights totalling 100 nights of EEG), we explored the optimal timing for stimulating spindles in an open-loop design where slow oscillation up-states were detected in real-time and stimulated with a short-duration pink noise (50ms). The results confirm that spindles are susceptible to sound, and explore how the physiological effects can be optimized by considering the spindle phase, and the amplitude envelope over the course of the spindle. Our results motivate the use of CLAS on sleep spindles to study their causal role in memory and learning. This research direction may lead to therapeutic interventions aiming to boost spindle activity, restore slow oscillation - spindle coupling that is degraded in older adulthood (Helfrich et al., 2018), and possibly improve memory outcomes.

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Poster

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ANID Fondecyt Postdoctorado 3200051
Deutsche Forschungsgemeinschaft (German Research Council, Tr-SFB 654 “Sleep and Plasticity”)

Title: Interplay between slow oscillations and spindles as a potential mechanism of odor-mediated memory cueing during sleep

Authors: D. M. BAUM[1,2], *A. SANCHEZ CORZO[3], J. G. KLINZING[5], R. SITARAM[4]; [1]Pontificia Univ. Catolica de Chile, Macul, Chile; [2]Inst. de Ingeniería Biológica y Médica, Macul, Chile; [4]Diagnos. Imaging, [3]St. Jude Children's Res. Hosp., Memphis, TN; [5]Inst. for Med. Psychology and Behavioural Neurobio., Univ. Tübingen, Tuebingen, Germany

Abstract: Memories are actively consolidated during sleep. This process is associated with specific neural activity patterns during Non-Rapid Eye Movement (NREM) sleep, such as Slow Oscillations, Sleep Spindles, and their temporal coordination (phase coupling). Memory consolidation can be enhanced using memory-associated sensory cues. This memory cueing technique is most commonly implemented using sounds but can also be performed with odors. Odor-mediated memory cueing has a variety of advantages but, compared to auditory cueing, its underlying neural mechanisms are yet to be fully described. Using a well-controlled, multi-odor within-subject experimental design, we investigated the neural activity associated with odor cueing of declarative memories during sleep. We recorded high-density electroencephalographic data from 23 participants during two experimental nights. In one night, we performed cueing with an odor that had previously been associated with a declarative memory task. The other night, the odor was associated with a motor task without a declarative learning component. We found that the declarative memory-associated odor triggered widespread increases in spindle rate and frontal spindle duration. Slow oscillation amplitude was increased over central areas. Furthermore, the rate of spindles was increased specifically around the up states of slow oscillations. Our results demonstrate the feasibility of studying memory type-specific brain responses to olfactory cueing. We identify sleep spindles, slow oscillations, and their coupling as the prime candidate mechanism behind memory cueing and thereby memory consolidation in general.

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Poster

PSTR305. Learning and Memory: Oscillations

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Program #/Poster #: PSTR305.07/WW21

Topic: H.08. Learning and Memory

Support: ANID Fondecyt Postdoctorado 3200051

Title: An easy-to-implement system to detect deep sleep and strategic time windows for memory strengthening

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Abstract: Memories can be modulated by playing memory-associated sounds during sleep, serving as semantic cues that induce strengthening of the memory contents. The efficacy of memory cueing relies on precise timing of the cues. Prior research has shown that optimal targets for auditory memory cueing are Slow Oscillation (SO) up states during Slow Wave Sleep (SWS). While auditory memory cueing has successfully been used in neuroscientific research, real-world applications are missing, partly due to the poor availability of easy-to-use and reliable implementations. Here, we present a closed-loop, cross-platform (PC and mobile) and context-aware system for memory cueing protocols. The system analyzes brain activity in real-time using a single EEG channel, detects SWS, and predicts upcoming SO up states for precise phase-locked cueing. We validated the system in a double-blinded and placebo-controlled experiment. Thirty participants learned the locations of 15 card pairs in a 2D object location task. For each pair, a specific sound was played and thereby associated with the memory of their location. During a subsequent nap, half of the sounds were presented again whenever the algorithm detected optimal time windows (SO up states during SWS). The other half of the card pairs was not cued. To control for unspecific effects of auditory cueing, placebo sounds (not associated with any cards) were presented randomly interleaved with the associated cues. After the nap, subjects showed significantly increased performance in locating cued cards compared to uncued ones. Offline electrophysiological analysis revealed that the system accurately detected SWS compared to sleep scoring performed by sleep experts or published classifiers (overall agreement between 71 ± 7 and 91 ± 3 % and false positive rates between 4 ± 1 % and 11 ± 4, average ± SEM). The system presented sounds during SO up states with a minimal error margin of 45 ± 17 ms (average ± SEM). In summary, we introduce an easy-to-use and portable system with reliable temporal precision for memory cueing protocols. As memory modulation is gaining interest in the therapeutic field, our algorithm may provide an efficient and portable tool for both scientific and clinical contexts.

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Poster

PSTR305. Learning and Memory: Oscillations

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Topic: H.08. Learning and Memory

Support: R01MH107512
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NINDS NS 21135

Title: Occipitotemporal alpha and theta dynamics support memory formation in the developing brain

Authors: *Q. YIN[1], E. JOHNSON[2], K. AUGUSTE[3,4], R. T. KNIGHT[5], E. ASANO[1,6], N. OFEN[1];
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Abstract: The ability to remember past experiences is critical for our daily life. The medial temporal lobe (MTL) is crucial for episodic memory and receives inputs from the occipital cortex to form memories for complex visual stimuli. However, the neurophysiological mechanisms underlying the interaction between these two regions in the developing brain are largely unknown. To understand the oscillatory mechanisms, we analyzed intracranial EEG data from 141 occipital and 71 MTL electrodes in 30 pediatric patients (6.2-20.5 years) who were undergoing direct cortical monitoring for seizure management. Subjects studied pictures of scenes by responding indoor/outdoor during 3-s scene presentation in preparation for a memory recognition test. First, we detected the dominant neural oscillations, i.e., oscillation with the largest peak, for each electrode between 1-15 Hz. Oscillation detection revealed that alpha dominates the occipital cortex (4.50 - 11.87 Hz, 8.43 ± 2.16 Hz), and theta dominates MTL (3.86 - 14.55 Hz, 7.22 ± 2.38 Hz). Critically, the oscillations in the occipital cortex were faster than those in MTL. No age effects were observed in oscillation frequencies for the occipital cortex or MTL. Second, we analyzed phase-amplitude coupling (PAC) between detected oscillations and high-frequency activity (HFA, 70 - 150 Hz), a mechanism posited to support information and mnemonic representation, as a function of subsequent recognition performance, i.e., subsequent hit vs. miss. In the occipital cortex, we observed increased alpha-HFA PAC on subsequent hit compared to miss trials after scene onset and before the indoor/outdoor response. Moreover, the positive PAC effects after scene onset positively correlated with recognition accuracy, and the positive PAC effects before the response increased with age. In MTL, we observed increased theta-HFA PAC on subsequent compared to miss trials before the response, and the positive

PAC effects increased with age. Third, we analyzed oscillation phase synchrony, a mechanism of inter-regional interaction, between the occipital cortex and MTL with the detected occipital alpha and MTL theta oscillations separately. We observed increased alpha and theta phase synchrony on subsequent hit compared to miss trials after scene onset and before the response. Moreover, the positive synchrony effects were higher in theta oscillations than in alpha. These results demonstrate the important role of alpha and theta oscillations in providing the functional infrastructure of memory in the developing brain by facilitating local processing and inter-regional interaction.

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Poster

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Topic: H.08. Learning and Memory

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Title: Temporal dynamics of memory encoding and retrieval in the human medial temporal lobe and prefrontal cortex

Authors: *A. J. O. DEDE[1], Z. R. CROSS[1], S. M. GRAY[4], Q. YIN[5], P. VAHIDI[5], E. ASANO[5], S. SCHUELE[2], J. ROSENOW[3], J. WU[3], S. LAM[3], J. RASKIN[3], J. J. LIN[6], O. K. MCMANUS[7], S. SATTAR[7], D. KING-STEPEHENS[8], P. WEBER[9], K. D. LAXER[9], E. F. CHANG[10], P. BRUNNER[11], J. L. ROLAND[12], R. T. KNIGHT[13], N. OFEN[5], E. L. JOHNSON[14];
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Abstract: The medial temporal lobe and prefrontal cortex coordinate their activity in the service of memory. However, the temporal dynamics of activity across these areas is not well understood. Here, we elucidate the relative timing of task-related activity in these regions during both memory encoding and retrieval. To do this, we analyzed intracranial electrophysiological recordings from 24 neurosurgical epilepsy patients (9 females, 15 males; age: 21.1 ± 4.4 years). All patients participated in a visual scene recognition memory task during intracranial

monitoring. Our regions of interest were the dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), parahippocampal and rhinal cortices (PHRC), and the hippocampus (HC). From an initial set of 223 electrodes across these regions, we selected only those with task-related high frequency broadband (HFB) responses - which index neuronal population activity - yielding 109 dlPFC channels, 39 ACC channels, 19 PHRC channels, and 30 HC channels. The peak latencies of HFB responses were submitted to linear mixed effects modeling using region, hit/miss memory performance, and encoding/retrieval task phase as fixed effects. Channel and subject ID were random effects. There was a significant encoding/retrieval by region interaction, which was largely driven by a shift in the timing of PHRC and HC responses. At encoding, PHRC and HC responses were 140ms faster than corresponding dlPFC and ACC responses. At retrieval, HC responses co-occurred with dlPFC and ACC responses, but PHRC responses sped up, leading the other three regions by 160ms. Looked at another way, we considered time between scene onset (t=0) and behavioral response (t=1) on a 0 to 1 scale. At encoding, the PHRC and HC exhibited peak activity at t=.41, compared to t=.50 for dlPFC and ACC. At retrieval, the HC, dlPFC, and ACC exhibited peak activity at t=.47-.49, whereas the PHRC led the other three regions at t=.39. These results suggest that during encoding, the HC functions as an extension of perception, encoding information as it arrives at the end of the visual hierarchy. By contrast, during retrieval, the HC functions as part of a top-down circuit involving the prefrontal cortex.

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Poster

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Topic: H.08. Learning and Memory

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R01NS21135

Title: Slow and fast theta signatures of memory formation within medial temporal lobe and their relationship with hippocampal volume

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Abstract: The medial temporal lobe (MTL) is crucial to episodic memory and is posited to support memory formation in children. However, the neurophysiological mechanisms by which different MTL regions support memory in the developing brain are unknown. We examined theta signatures of memory formation in the hippocampus (HC) as well as parahippocampal and rhinal cortices (PHRC) of individuals aged 5-28 years and related them to HC volumes. We capitalized on a rare opportunity to record intracranial EEG data from 35 neurosurgical patients (14F, 21M; 121 MTL electrodes) while they studied visual scenes, and indicated whether each scene was indoor/outdoor, in preparation for a memory recognition test. We observed positive correlations between HC volume, recognition performance, and age. After separating oscillatory components from aperiodic 1/f activity, we identified distinct slow (~2-4 Hz) and fast theta (~4-8 Hz) oscillations per electrode. We then identified slow and fast theta power and phase resetting signatures of memory formation by comparing subsequently remembered (hit) and forgotten (miss) scenes using linear mixed-effects models. Results showed positive effects (hit > miss) in (1) phase resetting at scene onset across theta frequencies and MTL regions, and (2) power prior to scene onset across theta frequencies and MTL regions. In HC, the latter effect was sustained following scene onset in the slow theta range, and as a function of HC volume in the fast theta range. Results also showed (3) a regional dissociation in power, with negative effects (hit < miss) observed around the indoor/outdoor response in PHRC but not HC. This dissociation is consistent with a growing body of literature in adults and points to a division of labor between adjacent MTL regions in the developing brain. Our results establish slow and fast theta signatures of memory formation within the developing MTL and begin to link MTL neurophysiology and HC structure to the development of episodic memory.

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Poster

PSTR305. Learning and Memory: Oscillations

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR305.11/WW24

Topic: H.08. Learning and Memory

Support: R00NS115918
R01NS21135

Title: Slow theta cross-frequency mechanisms in human hippocampus and amygdala differentially support working memory

Authors: *S. M. GRAY[1], J. J. LIN[2], I. SAEZ[3], F. GIRGIS[4], O. KIM-MCMANUS[5], S. SATTAR[5], E. F. CHANG[6], K. AUGUSTE[6], A. SHAIKHOUNI[7], R. T. KNIGHT[8], E. JOHNSON[9];
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Abstract: Cross-frequency phase-amplitude coupling (PAC) provides a neurophysiological mechanism by which information can be organized and maintained in working memory (WM). Theta-gamma PAC is consistently implicated during human WM maintenance, and PAC in the hippocampus (HC) has been shown to vary with WM load. Less is known about complementary roles of PAC during information encoding and maintenance, and across regions of hippocampal memory networks. Here, we examined stereo-EEG recordings of HC and amygdala (AMY) to delineate the role of PAC in adjacent medial temporal regions. Sixteen neurosurgical patients (6 females, 10 males; M ± SD, age: 29.8 ± 11.6 years) with electrodes sampling HC (n = 43) and/or AMY (n = 41) completed a WM delayed match-to-sample task in which they memorized sequences of three colored shapes (e.g., green triangle, purple square). We first computed event-related power from 1-200 Hz across correct trials, which identified low-frequency activity following presentation of the sample sequence in HC. We then segmented the data into 0.5s baseline, stimulus, and delay epochs and computed comodulograms (1-15 Hz phase, 20-200 Hz amplitude), z-score normalized on permuted data. PAC was identified between fast theta phase and slow gamma amplitude during the presentation and maintenance of the sample and test sequences in both regions (HC: 6.9-10.2 Hz phase, 32.8-53.7 Hz amplitude; AMY: 6.9-12.4 Hz phase, 23.6-45.5 Hz amplitude). In AMY but not HC, PAC between slow theta (2.2-3.9 Hz) phase and fast gamma (45.5-74.6 Hz) amplitude was increased during maintenance of the test compared to sample sequence (cluster-corrected p = 0.034). We last re-segmented the data into 3.25s sample and test epochs and computed oscillatory peaks in the slow and fast theta ranges. In HC but not AMY, slow theta slowed down from study to test (p = 0.014), consistent with longer slow theta cycles organizing additional information represented in gamma activity. These results are consistent with models of HC theta-gamma PAC in WM, highlight differential mechanisms by which HC and AMY may support WM, and raise the intriguing possibility that AMY supports WM for emotionally neutral information.

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Poster

PSTR305. Learning and Memory: Oscillations

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR305.12/WW25

Topic: H.08. Learning and Memory

Support: R00NS115918
R01NS21135

Title: Frontoparietal theta networks underlie the control of working memory

Authors: *L. SHI[1], K. CHATTOPADHYAY[2], V. KOMMU[2], S. GRAY[1], J. J. LIN[3], D. KING-STEPHENS[4,5], P. WEBER[4], K. D. LAXER[4], I. SAEZ[3,6], F. GIRGIS[3,7], E. CHANG[8], K. AUGUSTE[8,9], S. SCHUELE[1], J. M. ROSENOW[1], E. ASANO[10], R. T. KNIGHT[2], E. JOHNSON[1];
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Abstract: Research in the burgeoning field of network neuroscience yields a picture of how cognitive functions such as working memory (WM) arise from carefully orchestrated interactions among brain regions, particularly the prefrontal and lateral parietal cortices. Our integrative approach combines scalp electroencephalography (EEG) and intracranial EEG (iEEG) to investigate this complex interplay. In the first stage of our research, we used scalp EEG to capture brain activity from 35 healthy adults (18-43 years; 15 males, 20 females) engaged in a sequential WM delayed match-to-sample task. To isolate signatures of cognitive control (CC) with high temporal precision, we compared the sample and test (delayed match) sequences from correct trials using cluster-based permutation tests, keeping other variables including timing and visual demands the same. This analysis yielded two key results. First, CC-related fronto-posterior theta/alpha (4-15 Hz) event-related spectral power correlated with functional brain networks focused in the same channels. Second, CC-related fronto-posterior delta/theta (2-10 Hz) functional connectivity predicted behavioral outcomes, as indexed by both accuracy and response time. Building on these EEG findings, in the second stage we employ iEEG data from 20 epilepsy patients (15-54 years; 15 males, 5 females) with electrodes sampling one or both of prefrontal/anterior cingulate (n = 279) and parietal/posterior cingulate (n = 61) cortices. Our hypothesis, rooted in the observed EEG-based neural activity, postulates that the medial prefrontal and lateral parietal cortices are the sources of observed scalp effects, and their interplay supports successful WM performance. Our iEEG analyses address the inherent limitation of scalp EEG - its low spatial resolution. By examining electrodes in both medial and lateral prefrontal and parietal regions, this research enriches our understanding of the complex brain networks underpinning WM and contributes to the evolving landscape of network neuroscience.

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Poster

PSTR305. Learning and Memory: Oscillations

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Program #/Poster #: PSTR305.13/WW26

Topic: H.08. Learning and Memory

Support: R00NS115918
R01MH107512
R01NS21135

Title: Mapping human brain development in high definition using invasive electrophysiology

Authors: *Z. R. CROSS[1], S. M. GRAY[3], Q. YIN[4], P. VAHIDI[4], E. M. RAU[5], E. ASANO[6], J. LIN[7], O. MCMANUS[8], S. SATTAR[8], I. SAEZ[9], F. GIRGIS[10], D. KING-STEPHENS[11], P. WEBER[12], K. D. LAXER[12], S. SCHUELE[13], J. M. ROSENOW[2], J. Y. WU[14], S. LAM[15], J. RASKIN[14], K. I. AUGUSTE[16], E. CHANG[17], A. SHAIKHOUNI[18], P. BRUNNER[19], J. L. ROLAND[20], R. T. KNIGHT[21], N. OFEN[4], E. JOHNSON[1];
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Abstract: The human brain undergoes structural and functional changes during development that parallel changes in cognition. To date, developmental research has primarily used scalp electroencephalography (EEG), which offers low spatial resolution. Further, these studies have traditionally ignored aperiodic ($1/f$) activity, an index of excitation/inhibition (E/I) balance, which is associated with healthy aging compared to age-related cognitive decline and may be a critical marker of brain development. Here, we analyzed intracranial EEG (iEEG) data recorded directly from the brains of neurosurgical epilepsy patients. Using task-based (i.e., attention to-be-remembered visual stimuli) and task-free (resting-state) data from 73 children and adults (5.93 - 30 years, 29 females; *n* channels = 3371), we mapped functional brain development in high definition by quantifying the $1/f$ slope across the cortex. Mixed-effects regressions revealed a

significant non-linear relationship with age across the whole cortex during rest versus visual attention (β; = .58, se = .10, p <.001). From ages 5 - 15 years, for both rest and visual attention, the $1/f$ slope flattened linearly. By contrast, it continued to flatten linearly from ages 15 - 30 years during visual attention, while steepening during rest. We also found that key brain regions involved in visual attention and memory showed differential relationships between the $1/f$ slope, age, and attentional state. The $1/f$ slope flattened during visual attention in extrastriate cortex (rho = .54, p < .001) and angular gyrus (rho = .51, p < .001), but showed no association with age during rest. By contrast, the parahippocampal gyrus demonstrated a linear steepening of the $1/f$ slope from ages 5 - 30 during visual attention (rho = -.27, p = .003), while the inverse was observed during rest (rho = .33, p = .008). These findings indicate that E/I balance varies non-linearly across development and differs by attentional state across cortical region. Next, we will model oscillations from 1 - 30 Hz. To comprehensively characterize functional brain development, we will further relate regional $1/f$ slope and oscillations to grey matter volumes and memory outcomes.

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Poster

PSTR305. Learning and Memory: Oscillations

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR305.14/WW27

Topic: H.08. Learning and Memory

Support: R00NS115918

Title: Dissociable Fronto-Central Midline and Posterior Signatures of Mismatch Detection in Working Memory

Authors: ***J. B. YARBROUGH**[1], L. SHI[1], K. CHATTOPADHYAY[2], V. KOMMU[2], R. T. KNIGHT[3], E. JOHNSON[4];
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Abstract: Working memory (WM) is a form of higher order cognitive control in which one must rapidly store and retrieve incoming information. Although literature supports the role of frontal midline theta activity (θ; 3-8 Hz) in organizing signals of novelty and error in a top-down manner, it is unclear whether this applies to WM. Additionally, event-related potentials (ERPs) such as the N200 (associated with frontal midline) and P300 (associated with posterior

topography) are key indicators of error detection and visual perception, respectively. Here we investigate mismatch detection in WM to understand the neural substrate of mismatch detection in real-world scenarios. We recorded EEG from 35 healthy adults (20 females, 15 males; M ± SD, age: 25.3 ± 7 years) performing a delayed match-to-sample WM task. Participants were given a sample sequence of three shapes followed by one of four test sequences, and asked whether the test sequence was a match or a mismatch to the sample sequence. Participants performed well overall (M ± SD, accuracy [hit - false alarm rate]: 0.85 ± 0.13). To isolate signatures of mismatch detection, data from correct trials were aligned to the onset of the mismatched shape and compared to match trials using cluster-based permutation tests. We hypothesized that frontal midline θ and N200 ERPs would act as mechanisms for mismatch detection. We observed fronto-central midline (FCM) θ activity during mismatch detection, consistent with previous literature. Surprisingly, the N200 was not present. Instead, we observed FCM late positive potential ERPs, as well as sustained negative ERPs in right frontal and left posterior channels. ERPs did not correlate with θ or behavioral performance. Furthermore, we found that increased posterior alpha-beta phase resetting on match trials predicted behavioral performance. These findings reveal that mismatch detection in WM involves dissociable FCM and posterior mechanisms and suggest a novel late positive potential signature for error detection and higher order cognitive control.

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Poster

PSTR305. Learning and Memory: Oscillations

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Title: Identification of pathway-specific local field potentials in the entorhinal cortical-hippocampal networks

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Abstract: Input of neural oscillatory activities from other brain areas have been proposed to play a crucial role in the brain area-area communication, but there is a technical limitation to investigate its neural mechanism in a cell-type specific manner. Lesion experiments have traditionally been conducted, but they cannot elucidate the original dynamics of lesioned neural pathways. Recently, independent component analysis (ICA), a blind-source separation technique, has started to be used as a mathematical tool to disentangle local field potential (LFP) signals to specific input-pathway's activities. The conventional technique separates independent components (ICs) from original LFP by ICA, and speculates that the separated ICs are of the specific input-pathway using the anatomical location information of ICs (Fernández-Ruiz et al., J Neurosci. 2012, Schomburg et al., Neuron 2014; Fernández- Ruiz, et al., Neuron 2017). However, this method may not easily be applicable when multiple inputs are on the overlapping layers since spatial distributions of ICs will be similar in this case. Also, selecting an IC based on spatial distribution may have limited interpretation of the data since a single cell-type pathway may generate multiple ICs. To overcome these limitations, instead of using the anatomical locations information in the conventional method, we propose a new method to investigate input-pathway specific activities by optogenetically 'tagging' the pathway associated ICs. In the current study, a 32-ch silicon probe and an optical fiber were implanted into hippocampal CA1 of the mice expressing ChR2 in MECII pyramidal neurons or MECIII neurons to record spontaneous and opto-responded LFP. After ICs are separated from the LFP using ICA, they are categorized as "tagged" when the IC's opto-response exceed z-score threshold. Then, pathway associated LFPs are reconstruct from all "tagged" ICs. We also demonstrate simultaneous identification of two pathways in single mice, LEC and MEC to DG. Compared with the conventional method, our method has advantages of cell-type specific and less-biased analysis.

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Poster

PSTR305. Learning and Memory: Oscillations

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR305.16/WW29

Topic: H.08. Learning and Memory

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JSPS DC1 Research Fellowship for Young Scientists
JSPS Overseas Challenge Program for young Researchers

Title: Hippocampal neural representation of food intake episode

Authors: *Y. OMURA[1], J. YAMAMOTO[2], T. KITAMURA[1];
[1]Psychiatry | Neurosci., [2]Psychiatry, The Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: The temporal organization of neural activity is a fundamental representation underlying hippocampal cognitive processes of episodic memory. Cumulative evidence suggests that the hippocampus, which has long been considered as a neural substrate critical for navigation and episodic memory, has certain role in regulating food intake behaviors by encoding and retrieving food intake events (M.B. Parent et al., 2014). Recent studies have identified a dedicated hippocampal reward cell population which encodes arbitrary spatial locations of consummatory reward (J.L. Gauthier & D.W. Tank, 2018). However, how the hippocampus operates the encoding and retrieving of reward information to guide navigation remains elusive. Furthermore, although awake sharp wave ripples (SWRs) have been linked to learning, recent finding revealed that awake replay content was decoupled from subsequent choice in spatial memory task, indicating a role in memory storage rather than in guiding subsequent behavior (A.K. Gillespie et al., 2021). To elucidate a hippocampal role in linking food intake episode and subsequent navigation, we recorded neural activity from hippocampal dorsal CA1 of mice while performing a delayed non-matched to place (DNMP) task. Here, we identified three distinct subsets of reward cells, 1) ramping down cells, 2) midst cells, and 3) ramping up cells, which coordinately represented temporal dynamics of sequential nature of feeding behaviors, each of phasic activity encoded, 1) approaching food, 2) food consumption, and 3) meal termination. These reward subpopulations were modulated by 6-Hz theta oscillations during food consumption, emitting robust synchronous spiking outside SWR time window. Strikingly, we found that co-firing of the ramping down and up cells was significantly stronger during food consumption followed by correct choice trials than that followed by either error choice or sample trials. Contrarily, we did not observe the enhanced activation within SWRs followed by correct choice trials, indicating novel neural subsets which encode reward information to guide subsequent navigation.

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Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.01/WW30

Topic: H.08. Learning and Memory

Support: 1 R01 NS116051-01A1

Title: Loss of Neuron-Specific Gene 2 (NSG2) alters long-term potentiation, learning and memory

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Abstract: NSG2 is one of the three-member family of Neuron-specific genes (NSG1-3), which have been shown to regulate endolysosomal trafficking of a number of proteins critical for neuronal development and synaptic function. NSG2 is the least well-characterized of the family, but previous work in our laboratory has demonstrated binding to multiple AMPAR subunits and alterations in synaptic transmission following knockout and overexpression. Based on these studies, and the largely universal expression throughout mammalian brain, we predicted that genetic knockout of NSG2 would result in significant impairments across multiple behavioral modalities including motor, affective, and learning/memory paradigms. However, we were surprised to find that loss of NSG2 had highly selective effects on learning and memory modalities, leaving motor and affective behaviors intact. For instance, NSG2 knockout (KO) altered recall in the Morris water maze, without affecting acquisition rate during training. Similarly, NSG2 KO altered touchscreen reversal learning, but did not affect the initial acquisition phase of the association paradigm. In contrast, both acquisition and recall were significantly altered in a trace fear conditioning paradigm. Most surprising was the fact that in all cases where learning and memory were affected, loss of NSG2 caused *enhanced* recall and/or *accelerated* acquisition rather than impairments as predicted. These results paralleled alterations in Long-term potentiation (LTP) in acute brain slice preparations from hippocampus. Together, these data point to a specific involvement of NSG2 on certain types of associative learning, with endogenous NSG2 levels limiting the ability of particular circuits to create sensory-motor associations via changes in traditional models of synaptic plasticity.

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Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.02/WW31

Topic: H.08. Learning and Memory

Support: ARC Grant DP210103233

Title: Long noncoding RNAs modulate spatial learning and motor activity

Authors: *S. J. JUNG[1], M. W. LUQMAN[1], L. M. ITTNER[1], F. DELERUE[1], J. MATTICK[2];
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Abstract: Long noncoding RNAs (lncRNAs) are being shown to play major roles in developmental and cell biology (https://doi.org/10.1038/s41580-022-00566-8). The greatest

diversity of lncRNAs is found in the brain, with most exhibiting region- and cell-specific expression patterns, and association with subnuclear or cytoplasmic domains (https://doi.org/10.1073/pnas.0706729105). Their potential roles in governing brain functions are only starting to emerge. Here, we have examined the role of selected lncRNAs with brain area-specific expression patterns on cognitive, behavioral and motor tasks in multiple mouse lines using CRISPR-Cas9 genome editing. All lines were subjected to a battery of functional tests to assess memory and motor performance, including Morris water maze, novel object recognition, rotarod, beam, pole and grip strength test. We found that loss of different lncRNAs resulted in differential cognitive, learning and motor deficits. Our results demonstrate that lncRNAs contribute to executive brain functions like spatial learning and motor coordination in distinct and specific ways, providing new insights into the regulation of brain function.

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Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

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Program #/Poster #: PSTR306.03/WW32

Topic: H.08. Learning and Memory

Support: National Natural Science Foundation of China (32021002)
Peking University–Tsinghua University–National Institute of Biological Science Joint Graduate Program
Tsinghua–Peking Center for Life Sciences

Title: Social experiences switch states of memory engrams through regulating hippocampal Rac1 activity

Authors: B. LEI[1,2], L. LV[1,2], ***S. HU**[1,2], Y. TANG[1,2], Y. ZHONG[1,2];
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Abstract: In pathological or artificial conditions, memory can be formed as silenced engrams that are unavailable for retrieval by presenting conditioned stimuli but can be artificially switched into the latent state so that natural recall is allowed. However, it remains unclear whether such different states of engrams bear any physiological significance and can be switched through physiological mechanisms. Here, we show that an acute social reward experience switches the silent memory engram into the latent state. Conversely, an acute social stress causes transient forgetting via turning a latent memory engram into a silent state. Such emotion-driven bidirectional switching between latent and silent states of engrams is mediated through regulation of Rac1 activity-dependent reversible forgetting in the hippocampus, as stress-activated Rac1 suppresses retrieval, while reward recovers silenced memory under amnesia by inhibiting Rac1. Thus, data presented reveal hippocampal Rac1 activity as the basis for emotion-

mediated switching between latent and silent engrams to achieve emotion-driven behavioral flexibility.

Disclosures: **B. Lei:** None. **L. Lv:** None. **S. Hu:** None. **Y. Tang:** None. **Y. Zhong:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.04/WW33

Topic: H.08. Learning and Memory

Support: T32-NIA AG00099
1F32AG077872

Title: Crest can bidirectionally regulate memory processes of the adult hippocampus via its CBP binding domain

Authors: *F. G. GARCIA, M. F. DE ALBUQUERQUE, V. G. JOHNSON, E. A. KRAMÁR, D. P. MATHEOS, M. A. WOOD;
UC Irvine, Irvine, CA

Abstract: The epigenome provides a powerful signal-integration system for transforming learning-induced gene expression into molecular changes for consolidating new information into long-term memories. The discovery of Calcium-RESponsive Transactivator (CREST) has provided a key candidate for a transcriptional regulator with the capacity to recruit multiple epigenetic machinery for histone modification (via CBP; a histone acetyltransferase) and nucleosome remodeling (via BRG1-containing BAF complex). In this study we examined whether CREST, and its function as a keystone (bridging histone acetylation and nucleosome remodeling) transcriptional regulator, is essential for long-term memory formation and synaptic plasticity in the adult hippocampus. When we used an anti-Crest vivo morpholino oligomer for focal knockdown of CREST expression in the adult C57BL/6J hippocampus, both males and females showed impaired long-term memory for the object location memory task. Antisense-mediated Crest knockdown also revealed decreased potentiation in theta-burst induced LTP. Notably, Crest protein and mRNA expression do not change during memory consolidation, but motif analysis of CREST peptide sequence for posttranslational modifications revealed a candidate tyrosine 397 (Y397) residue within the CBP binding domain. The JetPEI-mediated in vivo transfection of a Crest phosphomimetic (Y397D) into the adult hippocampus was sufficient to enhance both memory formation under subthreshold training conditions and synaptic plasticity compared to vehicle controls. Alternatively, when we expressed a CREST phosphonull (Y397F) in the adult hippocampus, animals showed both impaired long-term memory formation with threshold training and synaptic plasticity. When Cbp-floxed mice with empty vector or Cre recombinase AAV infusion received intrahippocampal JetPEI-mediate expression of Crest Y397D and subjected to subthreshold training in the object location memory task, animals with

Cbp deletion and Crest Y397D infusion did not show evidence of long-term memory formation. Together, this study highlights a critical role for CREST in regulating hippocampal-dependent memory processes via post-translational modification and CBP-dependent signaling during memory consolidation.

Disclosures: F.G. Garcia: None. **M.F. De Albuquerque:** None. **V.G. Johnson:** None. **E.A. Kramár:** None. **D.P. Matheos:** None. **M.A. Wood:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.05/WW34

Topic: H.08. Learning and Memory

Title: Palmitoylated membrane protein 2 (MPP2) as a target for improving memory

Authors: *S. J. COHEN[1], R. W. STACKMAN, JR[2];
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Abstract: Episodic memory, the memory for personal events, is dependent upon a network of associated medial temporal lobe brain structures, including the hippocampus. Disturbances in hippocampal activity are associated with the memory impairments of Alzheimer's disease (AD). Progressive cognitive decline is a hallmark of AD, yet current treatment approaches are quite limited in efficacy to improve cognitive function. Discovering novel targets is essential in developing effective treatments for those suffering from learning and memory impairments. Thus, it is of broad interest to the field to better understand the neurophysiological and neuropathological changes that bring about age-related and AD-associated cognitive decline. Previous work has shown that the pharmacological blockade or genetic deletion of synaptic type 2 small conductance Ca2+-activated K+ (SK2) channels enhances hippocampal LTP and memory, while pharmacological activation or genetic overexpression of SK2 impairs LTP and memory. SK channels limit neurobiological mechanisms of long-term memory by shaping glutamatergic excitatory postsynaptic potentials and NMDA receptor-dependent synaptic plasticity within hippocampal and neocortical circuits that are critical for memory. SK channel activity also limits NMDA receptor mediated excitotoxicity. Membrane palmitoylated protein (MPP2) is a synaptic MAGUK scaffold protein that anchors SK2 channels in the postsynaptic density of hippocampal and cortical neurons. Our preliminary data indicate that knockdown of MPP2, via CRISPR/Cas9 gene editing, enhances glutamatergic excitatory postsynaptic potentials in the hippocampus, and improves spatial and non-spatial memory in adult male and female mice.

Disclosures: S.J. Cohen: None. **R.W. Stackman:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.06/WW35

Topic: H.08. Learning and Memory

Support: National Institute of Mental Health Grant No. MH107555
Brain and Behavior Research Foundation-NARSAD Independent Investigator Award
The NJ Governor's Council for Medical Research and Treatment of Autism
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R35 GM124976
NSF (DBI 1936046)
CONACYT (Mexico)
American Association of University Women (AAUW)

Title: Regulation of dopamine function by the gastrin-releasing peptide in stress-enhanced fear

Authors: *S. GONZALEZ[1], Y. MORISHITA[1], I. FUENTES[1], J. FAVATE[1], J. MEJAES[1], S. BUYSKE[1], S. SILLIVAN[2], C. A. MILLER[3], E. R. KANDEL[4], S. UCHIDA[5], D. BARKER[1], P. SHAH[1], G. P. SHUMYATSKY[1];
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Abstract: The role of dopamine in fear learning and extinction is poorly understood compared to its role in reward-related behavior. A core symptom observed in post-traumatic stress disorder and phobias are deficits in fear extinction. Thus, identification of molecules that regulate dopamine function in stress-related memories would help our understanding of the mechanisms behind post-traumatic stress disorder and phobias. Our lab found evidence that the gastrin-releasing peptide (Grp) regulates dopamine signaling during Stress-Enhanced Fear Learning (SEFL). A prior history of stress can enhance subsequent learning of conditioned fear, making it more resistant to extinction. SEFL is a behavioral assay used in mice to assess the effect of an acute stressor over fear acquisition and extinction. We generated the *Grp* gene knockout (*Grp*-/-) mice and found that they exhibit delayed fear extinction and enhanced long-term memory recall after SEFL. When examining candidate genes in the basolateral nucleus of the amygdala (BLA) following long-term memory recall of SEFL, we found that transcription of dopamine-related genes was decreased in *Grp*-/- mice. Using fiber photometry approach to record dopamine signals, we also found enhanced signal of the dLight sensor in the BLA of *Grp*-/- mice during training and extinction. Altogether, our data suggest that the Grp may regulate dopamine function during stress-enhanced fear learning and extinction.

Disclosures: **S. Gonzalez:** None. **Y. Morishita:** None. **I. Fuentes:** None. **J. Favate:** None. **J. Mejaes:** None. **S. Buyske:** None. **S. Sillivan:** None. **C.A. Miller:** None. **E.R. Kandel:** None. **S. Uchida:** None. **D. Barker:** None. **P. Shah:** None. **G.P. Shumyatsky:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.07/WW36

Topic: H.08. Learning and Memory

Support: NIH Grant R01MH116673
NIH Grant R21NS088421
NIH Grant R01NS115543

Title: Learning induces distinct modes of synaptic plasticity to balance memory discrimination and generalization

Authors: ***M. MENG**[1], J. DOUPE[1], D. FEITOSA TOMÉ[2], X. SUN[3], S. SADEH[2], C. CLOPATH[2], Y. LIN[1];
[1]Upstate Med. Univ., SYRACUSE, NY; [2]Imperial Col. London, London, United Kingdom; [3]Stanford Univ., Stanford, CA

Abstract: Memory engrams from past experiences are utilized to guide future behaviors, such as to discriminate or generalize contextual fear memory. Our recent study found that one way for the brain to achieve the balance between memory discrimination and generalization is to engage two distinct active neuronal ensembles within the contextual fear memory engram in the dentate gyrus (DG). These two active neuronal ensembles are each defined by the activation of the immediate-early gene *Fos* or *Npas4*, and they differentially drive the memory discrimination-generalization balance. We also found that they undergo distinct synaptic modifications following contextual learning. Synaptic modifications are believed to be the biological basis of memory. However, it is not known whether the distinct synaptic modifications associated with these two neuronal ensembles modulate memory expression differently. Here we show that *Fos* and *Npas4* directly regulate synaptic modifications beyond serving as markers of neuronal activity. *Fos* expression induced in a random population of neurons enhances excitatory drive onto those neurons, while *Npas4* expression recruits inhibitory inputs selectively from local cholecystokinin-expressing GABAergic interneurons onto *Npas4*-expressing neurons. These distinct synaptic reorganizations triggered by *Fos* and *Npas4* expression are consistent with synaptic modifications on *Fos*- and *Npas4*-dependent ensemble neurons after learning. In addition, we found that *Fos* knockout enhanced memory discrimination, whereas memory discrimination is impaired in the absence of *Npas4*. Finally, consistent with our experimental data, we developed a spiking network model that predicted that blocking *Fos*-mediated excitatory synaptic modifications or *Npas4*-mediated inhibitory synaptic modifications tips the balance of memory discrimination-generalization differently. These findings have not only

revealed critical roles of *Fos* and *Npas4* in mediating learning-induced synaptic plasticity, but also indicate that these synaptic modifications are responsible for the control of the memory discrimination-generalization balance.

Disclosures: M. Meng: None. **J. Doupe:** None. **D. Feitosa Tomé:** None. **X. Sun:** None. **S. Sadeh:** None. **C. Clopath:** None. **Y. Lin:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.08/WW37

Topic: H.08. Learning and Memory

Title: Pharmacologic activation of mTOR increases nucleolar activity and enhances memory

Authors: G. P. BAENA-CALDAS[1], M. REGIER[1], V. SEBASTIAN[1], J. KIM[3], C. ZHU[3], L. KOP[1], *J. LIBIEN[2], I. OJIMA[3], A. I. HERNANDEZ[1];
[1]Pathology, [2]SUNY - Downstate Hlth. Sci. Univ., Brooklyn, NY; [3]Chem., SUNY - Stony Brook, Stony Brook, NY

Abstract: The Mammalian Target of Rapamycin (mTOR) is composed of 2 different complexes (mTORC1 and 2) with distinct roles in mammalian cells. mTOR integrates diverse environmental signals in cells to respond to growth (mTORC1) or survival and proliferation (mTORC2). The role of TORC1 in synaptic plasticity dependent translation and RNA Pol II dependent transcription has been intensively studied. In contrast, the role of TORC1 activation of RNA Pol-I (Pol-I) dependent transcription and subsequent biogenesis of ribosomes in synaptic plasticity and learning and memory remains unexplored. Recently, we found that memory consolidation requires Pol-I dependent transcription, and therefore newly synthesized ribosomes. Since mTORC1 regulates growth including the biogenesis of ribosomes we asked: 1) can ectopic activation of mTORC1 have an effect in learning and memory beyond normal? and 2) Do mTORC1 changes in learning and memory require the biogenesis of ribosomes? In light of this, we seek to investigate the effect of mTORC1 activation by 3-benzyl-5-((2-nitrophenoxy) methyl)-dihydrofuran-2(3H)-one (3BDO) on learning and memory. Here, we show that a single dose of 3BDO shortly before a weak training accelerates learning and enhances 24 h long-term memory. These observations correlate with nucleolar activation.

Disclosures: G.P. Baena-Caldas: None. **M. Regier:** None. **V. Sebastian:** None. **J. kim:** None. **C. zhu:** None. **L. Kop:** None. **J. Libien:** None. **I. Ojima:** None. **A.I. Hernandez:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.09/WW38

Topic: H.08. Learning and Memory

Support: Robert Wood Johnson Foundation AMFDP Award
CHOC Internal Pilot Award
Child Neurology Foundation Elterman Award
Department of Pediatrics, UC Irvine

Title: Neural epigenetic mechanisms of early life adversity and exercise intervention: a potential role for KDM7a.

Authors: N. E. NELSON[1], **S. VERMA**[2], A. MALIK[2], A. O. AGYEMANG[3], *A. S. IVY[4,5]; [1]Physiol. & Biophysics, Univ. of California, Irvine, Irvine, CA; [2]Biol. Sci., Univ. of California Irvine, Irvine, CA; [3]Pediatrics, Univ. of California- Irvine, Irvine, CA; [4]Univ. California-Irvine, Irvine, CA; [5]Neurol., Children's Hosp. Orange County, Orange, CA

Abstract: Background: Early-life adversity (ELA) can lead to long-term cognitive impairments, yet effective treatments to buffer against these consequences do not exist. Physical activity during adolescence can promote long term memory and enhance synaptic plasticity; thus, our experiments introduce adolescent exercise as a possible intervention after ELA. Our previously published data demonstrate that voluntary wheel running (Early Ex) during the 4th-6th postnatal weeks in mice results in lasting improvements in hippocampal memory and synaptic plasticity. Furthermore, we identified unique molecular signatures of Early Ex using TRAP-Seq analysis of translating mRNA expression. This included significant increases in hippocampal neuronal expression of multiple histone modifying enzymes, including the lysine demethylase KDM7A. *We hypothesize that Early Ex promotes a transcriptionally permissive epigenetic state via the activity of KDM7A, which may underlie the beneficial effects of Early Ex to mitigate cognitive impairments after ELA.* **Approach:** Emx1-cre female mice were crossed with NuTRAP reporter males (Raus et al., 2023) to generate experimental animals. Male and female Emx1-NuTRAP mice underwent ELA during postnatal days (P) 2-9 which consisted of limiting bedding and nesting material in the cage. On P21, a subset of juvenile mice were pair-housed in running wheel-equipped cages and running distances were monitored until P41. After removal from running cages on P42, mice underwent a battery of hippocampus dependent and independent behavior tasks in adulthood. Mice were sacrificed at P21, P42, or adulthood, and bilateral dorsal hippocampi were collected for molecular studies including mass spectrometry, RT-qPCR and western blot analysis to identify epigenetic signatures associated with ELA and Early Ex. **Results:** Object location memory was impaired in ELA mice, and partially rescued by Early Ex intervention. Mass-spec revealed opposing histone modification signatures of ELA and Early Ex. Specifically, the methylation status at H3K27 was uniquely altered depending on the early life experience (adversity vs. exercise). H3K27me2 state was found in a higher abundance in ELA, whereas in Early Ex the H3K27me1 and me3 state were found in a higher abundance. This specific histone residue is demethylated by KDM7a, which is increased after Early Ex, and may be responsible for this experience-induced epigenetic signature. **Conclusion:** These data implicate an epigenetic mechanism by which early exercise modulates hippocampal long term memory functions in adulthood, potentially through KDM7A activity on H3K27.

Disclosures: **N.E. Nelson:** None. **S. Verma:** None. **A. Malik:** None. **A.O. Agyemang:** None. **A.S. Ivy:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.10/WW39

Topic: H.08. Learning and Memory

Support: NIH/NINDS NS091144
Aligning Science Across Parkinson's ASAP-020551
Stanford School of Medicine Dean's Postdoctoral Fellowship
Parkinson's Foundation Postdoctoral Fellowship
Brain & Behavior Research Foundation

Title: Motor learning induced transcriptomic changes in motor engram neurons

Authors: *Y. SUN, R. H. ROTH, F.-J. HWANG, X. REN, S. WANG, J. B. DING;
Stanford Univ., Stanford, CA

Abstract: Motor learning induces profound dynamic reorganization of structure and activity in primary motor cortical (M1) neurons and striatal spiny projection neurons (SPNs). However, the molecular profile of motor engram cells and the underlying transcriptome regulation mechanism induced by motor learning remain unclear. Here, we combined activity-dependent genetic labeling tools (TRAP mice) and single cell RNA sequencing (scRNA-seq) to identify cell types and gene expression regulation mechanisms involved in motor learning and memory formation. TRAP mice were trained in a forelimb reaching task, and specifically activated cells in early and late training stages were TRAPed. Through scRNA-seq analysis, we identified TRAPed engram neurons in various neuronal populations, including glutamatergic corticostriatal projection neurons, and various types of GABAerigic interneurons. By quantifying the percentage of TRAP cells in each cell type, we investigated preferential activation during different stages of motor learning. Notably, we observed significant changes in the activation of a specific M1 interneuron type expressing 5-Hydroxytryptamine receptor 3a (Htr3a-Int). Using 2-photon Ca^{2+} imaging, we observed a selective Htr3a-Int activity coupled with reaching behavior. Furthermore, we detected significant differential expression of genes associated with synaptic functions and movement disorders during early and late learning stages in M1 and SPNs. Our scTRAP-seq findings, coupled with subsequent validations, identified novel cell types in corticostriatal circuits involved in motor learning, and provided mechanistic insights into coordinated pre- and postsynaptic gene expressions regulating synaptic plasticity induced by motor learning.

Disclosures: **Y. Sun:** None. **R.H. Roth:** None. **F. Hwang:** None. **X. Ren:** None. **S. Wang:** None. **J.B. Ding:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.11/WW40

Topic: H.08. Learning and Memory

Title: Enhancement of cognitive function through HDAC inhibitor at dose increasing gene expression

Authors: K. MIYAMOTO, K. UNEMURA, K. HYAKKOKU, T. IZUMI, T. HATTA, N. SUZUKI, M. ITO, K.-I. KUSAKABE, *K. OGAWA, N. HORIGUCHI;
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Abstract: Histone acetylation, particularly of histone H4K12, plays a crucial role in positively regulating gene expression, which is vital for various physiological functions, including learning and memory. Non-clinical studies using histone deacetylase (HDAC) inhibitors, the enzyme that causes histone deacetylation, have shown enhanced cognitive function, and increased spine number and density. However, the details of mechanisms and optimal dosage to show maximal efficacy remain unclear. In this study, we investigated gene alterations and their effects on cognitive function following HDAC inhibition using CI-994, a class I selective HDAC inhibitor. Oral administration of CI-994 in mice led to a dose-dependent increase in H4K12 acetylation and HDAC inhibition rate in the hippocampus. We then quantified gene alterations in the hippocampus after CI-994 administration at several dose. We demonstrated a transient increase of *cnih3* gene, which encodes for the auxiliary subunit protein of AMPA receptors, peaked at 7 hours after administration. AMPA receptors are known to play a significant role in the maintenance of long-term potentiation (LTP) induced following a learning stimulus. We hypothesized that aligning the peak of *cnih3* increase with the few hours from learning stimulus would efficiently induce cognitive function. When mice were given CI-994 four hours before a foot shock learning stimulus to align the peak of *cnih3* expression with three hours after stimulus, the freezing ratio in the recall test 24 hours after the foot shock increased in a dose-dependent manner. In contrast, administration of CI-994 four hours after the foot shock did not change the freezing ratio in the recall test. These results suggest that the increase and timing of *cnih3* expression could be important for enhancing learning and memory associated with HDAC inhibition. This study indicates the potential to define the optimal dosage of HDAC inhibitors by focusing on changes in gene expression as part of downstream mechanisms.

Disclosures: K. Miyamoto: A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **K. Unemura:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **K. Hyakkoku:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **T. Izumi:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **T. Hatta:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **N. Suzuki:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **M. Ito:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **K. Kusakabe:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **K. Ogawa:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd. **N. Horiguchi:** A. Employment/Salary (full or part-time):; Shionogi & Co.,Ltd..

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.12/WW41

Topic: H.08. Learning and Memory

Title: Defining the transcriptomic architecture of memory in the mouse hippocampus

Authors: *I. P. VINGAN[1], S. PHATARPEKAR[2], V. S. K. TUNG[3], M. HUNTER[5], O. EVGRAFOV[4], J. M. ALARCON[6];
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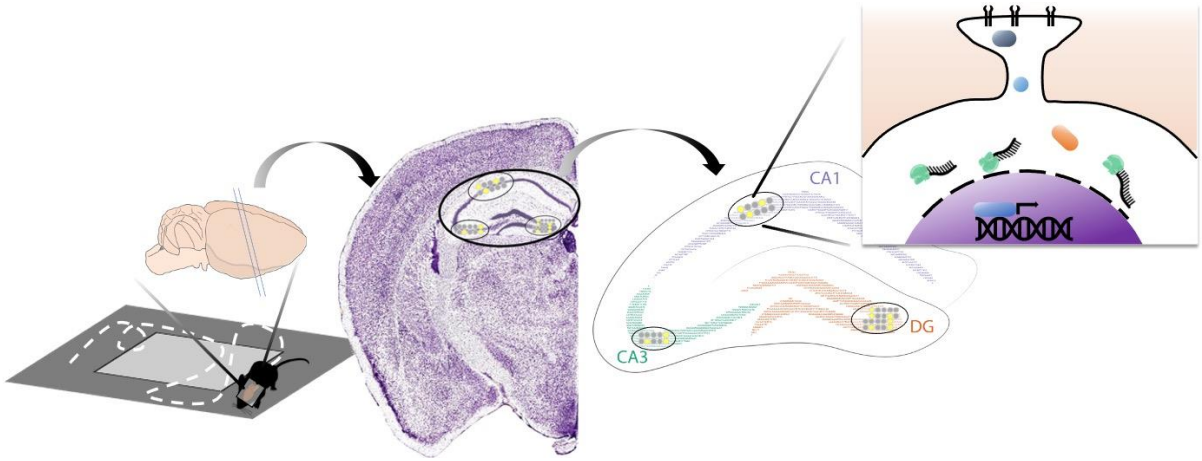
Abstract: The search for the memory engram has been a defining endeavor for the field of neuroscience. In the mammalian brain, the field has identified synaptic plasticity as a core mechanism for memory, and the coordinated activity of ensembles of neurons within relevant brain structures as the functional neuronal correlate for a memory trace (i.e., memory-associated neuronal ensembles). While the mechanistic basis of the engram is well-defined (i.e., synaptic plasticity), its mechanistic organization - the arrangement of molecular mechanisms supporting the memory trace within an neuronal ensemble - remains elusive. We wish to tackle this unknown by exploring the gene expression topography of hippocampal memory traces. Our goal is to identify and map networks of gene expression within memory-associated neuronal ensembles across the hippocampal network. The specific objective of this project is to explore whether gene expression profiles identified within memory-associated, immediate-early gene tagged neuronal ensembles exhibit different patterns of expression across the distinct sub-regions of the hippocampal network. We collected hippocampal tissue from mice trained in an active place avoidance memory task for RNA sequencing analyses. Samples were processed through: microdissected bulk RNA-seq and single nuclei RNA-seq to test for specific differences between hippocampal cells and regions; or spatial transcriptomics to assess the spatial distribution of gene expression profiles across the hippocampus. With these data we resolve the spatial organization of memory-associated gene expression profiles in the hippocampal network and provide a hitherto unknown gene expression map of memory, closing the gap between the molecular and network scales of memory.



Disclosures: **I.P. Vingan:** None. **S. Phatarpekar:** None. **V.S.K. Tung:** None. **M. Hunter:** None. **O. Evgrafov:** None. **J.M. Alarcon:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.13/WW42

Topic: H.08. Learning and Memory

Support: Else Kröner-Promotionskolleg JSAM
Marie Sklodowska-Curie grant agreement no. 859890 (SmartAge)
IMPULS, Carl Zeiss Foundation: P2019-01-006

Title: Voluntary wheel running in old mice reduces age-related inflammation in the colon

Authors: M.-L. EDERER[1], M. GÜNTHER[3], L. BEST[4], J. LINDNER[2], C. KALETA[4], O. W. WITTE[3], R. SIMON[1], ***C. FRAHM**[1];
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Abstract: Inflammation is considered a possible cause of cognitive decline during aging. This study investigates the influence of physical activity and social isolation in old mice on their cognitive functions and inflammation. The Barnes maze task was performed to assess spatial learning and memory in 3, 9, 15, 24, and 28 months old male C57BL/6 mice as well as following voluntary wheel running (VWR) and social isolation (SI) in 20 months old mice. Inflammatory gene expression was analyzed in hippocampal and colonic samples by qPCR. Cognitive decline occurs in mice between 15 and 24 months of age. VWR improved cognitive functions while SI had negative effects. Expression of inflammatory markers changed during aging in the hippocampus (Il1a/Il6/S100b/Iba1/Adgre1/Cd68/Itgam) and colon (Tnf/Il6/Il1ra/P2rx7). VWR attenuates inflammaging specifically in the colon (Ifng/Il10/Ccl2/S100b/Iba1), while SI regulates

intestinal Il1b and Gfap. Inflammatory markers in the hippocampus were not altered following VWR and SI. The main finding of our study is that both the hippocampus and colon exhibit an increase in inflammatory markers during aging, and that voluntary wheel running in old age exclusively attenuates intestinal inflammation. Based on the existence of the gut-brain axis, our results extend therapeutic approaches preserving cognitive functions in the elderly to the colon.

Disclosures: **M. Ederer:** None. **M. Günther:** None. **L. Best:** None. **J. Lindner:** None. **C. Kaleta:** None. **O.W. Witte:** None. **R. Simon:** None. **C. Frahm:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.14/WW43

Topic: H.08. Learning and Memory

Support: MRC project grant MR/V013173/1

Title: Long term memory consolidation in the hippocampus require the histone lysine demethylase KDM5B

Authors: L. PEREZ-SISQUES[1], S. BHATT[1], R. MATULEVICIUTE[1], T. GILEADI[1], E. A. KRAMÁR[3], A. GRAHAM[1], F. GARCIA[5], A. A. KEISER[4], D. P. MATHEOS[6], J. A. CAIN[1], A. PITTMAN[7], C. FERNANDES[2], M. A. WOOD[8], K. GIESE[1], ***M. BASSON**[9];
[2]MRC Social, Genet. & Developmental Psychiatry Ctr., [1]King's Col. London, London, United Kingdom; [3]Neurobio. and Behavior and Ctr. for the Neurobio. of Learning & Memory, [4]Univ. of California, Irvine, Univ. of California, Irvine, Irvine, CA; [5]UC Irvine, Irvine, CA; [6]Univ. of California, Irvine, CA; [7]St. George's Univ. of London, London, United Kingdom; [8]Neurobiol & Behavior, Univ. Calif, Irvine, IRVINE, CA; [9]Clin. and Biomed. Sci., Univ. of Exeter, Exeter, United Kingdom

Abstract: The histone lysine demethylase KDM5B has been implicated in recessive intellectual disability disorders and heterozygous, protein truncating variants in KDM5B are associated with reduced cognitive function in the normal adult population. The KDM5 family of lysine demethylases have developmental as well as homeostatic functions in the nervous system, some of which appear to be independent of lysine demethylase activity. In an attempt to distinguish between developmental and demethylase-dependent functions of KDM5B in hippocampus-dependent learning and memory, we studied mice homozygous for a *Kdm5b* allele (*Kdm5b*$^{\Delta ARID}$) that lacks demethylase activity and knocked down *Kdm5b* specifically in the adult, wildtype mouse hippocampus with shRNA. Demethylase-deficient *Kdm5b*$^{\Delta ARID/\Delta ARID}$ mice exhibited hyperactivity, mild anxiety, and long-term memory deficits in hippocampus-dependent learning tasks. The expression of immediate early, activity-dependent genes was downregulated in mice in the home cage (baseline) and hyperactivated upon a learning stimulus compared to wildtype mice. The expression of other learning-associated genes was also significantly altered in the

Kdm5b$^{\Delta ARID/\Delta ARID}$ hippocampus. *Kdm5b* knockdown in the dorsal hippocampus of adult, wildtype mice resulted in the induction of spontaneous seizures, hyperactivity and hippocampus-dependent long-term memory and LTP deficits. We conclude that KDM5B has a critical, direct function in regulating memory consolidation in the adult hippocampus. Together, these findings suggest that at least some of the cognitive deficits associated with KDM5B deficiency could be amenable to treatment in adults.

Disclosures: **L. Perez-Sisques:** None. **S. Bhatt:** None. **R. Matuleviciute:** None. **T. Gileadi:** None. **E.A. Kramár:** None. **A. Graham:** None. **F. Garcia:** None. **A.A. Keiser:** None. **D.P. Matheos:** None. **J.A. Cain:** None. **A. Pittman:** None. **C. Fernandes:** None. **M.A. Wood:** None. **K. Giese:** None. **M. Basson:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.15/WW44

Topic: H.08. Learning and Memory

Support: DNRF grant 133

Title: Behavioral and transcriptomic analysis of Grin2b-3'UTR deletion mouse model

Authors: *A. HARVEY, P. NISSEN, M. KJÆRGAARD, H. POULSEN;
Mol. Biol. & Genet., Aarhus Univ., Aarhus C, Denmark

Abstract: NMDA Receptors (NMDARs) are calcium-permeable channels that drive learning and memory by activating downstream signaling pathways in a process called synaptic plasticity. The mRNA of the NMDAR2B subunit (*Grin2b)*, a known driver of neuronal development and differentiation, contains an unusually long 3'-untranslated region (3'UTR) of nearly 20kb, approximately 20 times the average mammalian 3'UTR length, but its exact role remains unknown. Many studies show that particular plasticity-related transcripts are trafficked to activated synapses for local protein synthesis, and in several cases, the process depends on RNA-binding proteins (RBPs) interacting with regulatory motifs in the 3'UTR. Recent evidence suggests that NMDAR transcripts are also trafficked to dendrites, but it is not clear what role local NMDAR protein synthesis may have. This study aims to better understand the post-transcriptional regulation of *Grin2b* mRNAs and how they may be transported in neurons. To investigate this novel concept of gene regulation, we have developed a mouse model, which harbors an 19kb deletion of the *Grin2b*-3'UTR, leaving the protein coding region unperturbed. In these mice we integrate animal behavioral evaluation with transcriptomic and proteomic analysis from hippocampal and cortical tissue. We find behavior deficits in 3'UTR knockout mice with underlying gene expression and proteomic changes. This marks the first assessment of the effect of the *Grin2b*-3'UTR deletion in adult mice, and further characterization of the expression

patterns and localization dynamics in this mouse model will aid in a better understanding of the post-transcriptional mechanisms that underlie synaptic plasticity.

Disclosures: **A. Harvey:** None. **P. Nissen:** None. **M. Kjærgaard:** None. **H. Poulsen:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.16/WW45

Topic: H.08. Learning and Memory

Support: Fujian Medical University Postgraduate Academic Exchange Fund 2022QH2001

Title: Mechanism of Padi2-mediated vimentin citrullination to promote microglial activation in the pathogenesis of AD

Authors: *J. ZHANG[1], J. ZHANG[2];
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[2]Fujian Med. university, Fuzhou, China

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive impairment. The state and function of microglia play a key role in the occurrence and development of AD, making it important to investigate the reasons for microglia activation in early-stage AD. Citrullinated vimentin is typically found in the periphery, however, studies have found high expression of Padi2 and the presence of citrullinated vimentin in the brains of AD patients. To determine whether the high expression of Padi2 in AD mediates citrullinated vimentin, thereby promoting microglia activation and accelerating the occurrence and progression of AD, we first detected citrullinated vimentin in the hippocampus and cortex of young 5xFAD mice using mass spectrometry and western blot . Subsequently, we observed significant activation of primary microglia when they treated with citrullinated vimentin .When we injected with citrullinated vimentin in mice through the lateral ventricle, the mice showed impaired cognitive function and reduced postsynaptic density protein 95 (PSD95), a synaptic marker. When we administered a specific inhibitor of Padi2 to the mice, we found a significant reduction in citrullinated vimentin, along with a marked improvement in cognitive function. Our study reveals that Padi2-mediated citrullinated vimentin is a novel molecular driver of early-stage microglia activation in AD, which may provide new targets for the prevention and treatment of AD.

Disclosures: **J. Zhang:** None. **J. Zhang:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.17/WW46

Topic: H.08. Learning and Memory

Support: CONACYT

Title: Maternal nutritional programming enhance microglia phagocytosis leading to cognitive decline in 6-moth old male mice

Authors: *S. BERNAL-VEGA[1,2], M. CARDENAS-TUEME[1,4], D. RESÉNDEZ -PÉREZ[5], A. CAMACHO[3];
[1]Univ. Autónoma de Nuevo Leon, San Nicolás de los Garza, Mexico; [2]Neurometabolism Unit, Ctr. for Res. and Develop. in Hlth. Sci., Univ. Autónoma De Nuevo León, Monterrey, Mexico; [3]Univ. Autónoma De Nuevo León, Nuevo León, Mexico; [4]Sch. of Med. and Hlth. Sci., Tecnologico de Monterrey, Monterrey, Mexico; [5]Dept. of Cell Biol. and Genet., Univ. Autónoma de Nuevo León, San Nicolás de los Garza, Mexico

Abstract: Cognitive aging refers to the natural decline in brain processing and tasks that occurs with advancing age. It has been proposed that the presence of an inflammatory profile leads to the progression of cognitive impairment through increased levels of circulating proinflammatory cytokines and activation of microglial cells at the central nervous system. Although the molecular pathways that triggers systemic and central inflammation during aging are not clearly defined, several studies had shown that exposure to a hypercaloric diet may favor a proinflammatory state at earlier times than those observed in physiological aging. For example, our research group has identified that exposure of female mice to hypercaloric diet during pregnancy and lactation induces activation of microglial cells in the hypothalamus and increased systemic and central proinflammatory profile in the offspring. We identify whether nutritional programming with hypercaloric diet favors the onset of cognitive impairment at early ages through increased microglial phagocytosis. We exposed female C57/BL6J mice to a cafeteria diet for 9 weeks, and their male offspring of 2 and 6 months of age were cognitively evaluated using behavioral tests to determine deficits in memory and learning. Next, primary culture of microglia were obtained from hippocampus and cortex, phagocytosis was determined using myelin stained with BODIPY , the percentage of phagocytic cells was analyzed using flow cytometry. The results obtained show that nutritional programming increases the susceptibility of the offspring to present impaired spatial, recognition and working memory through increased phagocytic activity of hippocampal and cerebral cortex microglia at 6 months. We propose that Maternal nutritional programming could increase the phagocytic activity of microglia eliminating functional synapses and contributing to the development of cognitive impairment early in life

Disclosures: S. Bernal-Vega: None. **M. Cardenas-Tueme:** None. **D. Reséndez -Pérez:** None. **A. Camacho:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.18/WW47

Topic: H.08. Learning and Memory

Support: NIH DA053261

Title: Deletion of $Ca_v1.2$ from D1R expressing neurons is associated with sex-specific effects on long-term memory

Authors: *D. SCALA CHAVEZ[1], A. SEUNGHYUNG LEE[1], A. MARTINEZ-RIVERA[2], A. M. RAJADHYAKSHA[3];
[1]Pediatric Neurol., Cornell University: Weill Cornell Med. Col., New York, NY; [2]Weill Cornell Med., New York, NY; [3]Joan and Sanford I Weill Med. Col. of Cornell Univ., New York, NY

Abstract: Dopamine signaling plays a key role in a variety of neuropsychiatric-related conditions including cognitive and emotional impairments. One downstream target of dopamine signaling is the $Ca_v1.2$ isoform of the L-type calcium channel. A variety of genome-wide association studies have found that single nucleotide polymorphisms (SNPs) of *CACNA1C*, the gene that codes for $Ca_v1.2$, are associated with schizophrenia, bipolar disorder, and a variety of other neuropsychiatric disorders. A previous study from our lab has shown that deletion of $Ca_v1.2$ channels in D1-expressing neurons (D1-Cre; $Ca_v1.2^{fl/fl}$) causes heightened contextual fear memory at long-term time points in male mice. To assess additional characteristics of these mice and potential sex-specific behavioral phenotypes, we performed a battery of behaviors. Here we report that deletion of $Ca_v1.2$ in D1-expressing neurons causes heightened contextual fear memory in both male and female mice when tested 30 days later, replicating and adding to our lab's previous findings. Of interest, females show higher sensitivity to the contextual fear, as the phenotype is present in heterozygote females (D1-Cre; $Ca_v1.2^{fl/+}$) but not males. Alongside these findings, we also report that deletion of $Ca_v1.2$ in D1-expressing neurons causes impaired learning in male but not female mice in the Water Y-maze task. Training consisted of five one-minute trials on day 1, with subsequent memory tests on days 2 and 7 post-training. At day 7, male heterozygous and homozygous mice showed significantly higher latency to find the platform compared to their wildtype counterparts. Female heterozygous and homozygous mice performed similar to wildtype mice. All groups reported normal locomotor activity, and there were no significant differences in social behavior or anxiety-like behavior, which we tested using the 3-chamber social assay and the elevated plus maze, respectively. Our results suggest that there are sex dependent effects of D1- $Ca_v1.2$ regulation and suggests that the male D1 expressing neurons modulate $Ca_v1.2$ differently than their female counterparts. Further studies will elucidate the brain region, circuit and molecular mechanisms that drive the sex-specific behavioral phenotypes in mice lacking $Ca_v1.2$ in D1-expressing cells. All experiments include a sample size of 7 or more animals, and differences among treated groups were established after performing the corresponding statistical analyses with significance defined as p values less than 0.05.

Disclosures: **D. Scala Chavez:** None. **A. Seunghyung Lee:** None. **A. Martinez-Rivera:** None. **A.M. Rajadhyaksha:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.19/WW48

Topic: H.08. Learning and Memory

Support: NIDCD R01 DC-018561

Title: Sound reward learning induces spatially distinct auditory cortical transcriptional changes identified by cortical layer and cell type

Authors: *G.-E. GRAHAM[1,2], L. CO[2], A. KANDUKURI[2], M. SUMNER[2], M. S. CHIMENTI[3], K. L. KNUDTSON[3], D. GRENARD[2], K. M. BIESZCZAD[4];
[2]Behavioral and Systems Neuroscience, Dept. of Psychology, [1]Rutgers Univ., Piscataway, NJ; [3]Iowa Inst. of Human Genet., Univ. of Iowa Carver Col. of Med., Iowa City, IA; [4]Psychology, Behavioral and Systems Neurosci., Rutgers The State Univ. of New Jersey, Piscataway, NJ

Abstract: Experience-dependent mechanisms underlying neurophysiological plasticity are required for the formation of long-term memories (LTMs). Epigenetic mechanisms are powerful experience-dependent regulators of gene expression needed for the processing of LTMs. One such epigenetic regulator, histone deacetylase 3 (HDAC3) works with transcriptional machinery to influence activity-dependent *de novo* DNA transcription. We build upon previous studies detailing increased auditory cortical plasticity and sound-specific behavior with HDAC3 inhibition (HDAC3i) by providing insight to molecular mechanisms underlying these changes. Our results reveal the auditory cortical effects of inhibiting HDAC3 in adult male rats during early acquisition of an auditory associative task (sound-reward learning) at the transcriptomic level. On a genome-wide scale, we found that HDAC3i produced large changes in learning-dependent transcription by further up- or down-regulating unique subsets of induced genes (relative to vehicle and sound-naïve groups). qRT-PCR performed on a separate cohort of animals that performed the same behavioral task verified effects seen in identified genes of interest (GOIs). While this work achieved bulk analysis of the auditory cortical transcriptome during learning, further investigation was needed to relate these profiles to cellular identity. To achieve anatomical specificity of gene expression events, we utilized single molecule fluorescent *in situ* hybridization (smFISH) to visualize GOI mRNA transcripts. Presumptive target genes regulated by HDAC3 identified from bulk RNAseq *Egr1*, *Per2*, and *Chrna7* were characterized within cortical tissue from a third cohort of animals that experienced the same sound-reward learning paradigm. GOI transcripts were colocalized with *CamkIIa* and *Rorb* transcripts to identify transcriptional changes within excitatory pyramidal cells and different cortical layers. Our findings characterize how HDAC3 regulates genes within subpopulations of cells to begin to

understand how changes in local cortical microcircuitry can support highly precise and lasting associative memories.

Disclosures: G. Graham: None. **L. Co:** None. **A. Kandukuri:** None. **M. Sumner:** None. **M.S. Chimenti:** None. **K.L. Knudtson:** None. **D. Grenard:** None. **K.M. Bieszczad:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.20/WW49

Topic: H.08. Learning and Memory

Support: NIH Grant 1R01AG056622-01

Title: Effects of neuronal p27 genetic suppression on memory and cognition

Authors: *J. V. PATEL[1], X. WANG[2], X. ZHOU[3], T. MA[4];
[1]Intrnl. Med. – Geriatrics, Wake Forest Univ. Sch. Of Med. Neurosci. Program, Winston-Salem, NC; [2]Intrnl. Med. – Geriatrics, Wake Forest Univ. Sch. of Med., Winston Salem, NC; [3]Intrnl. Med. – Geriatrics, Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [4]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC

Abstract: p27 is a cyclin-dependent kinase (CDK) inhibitor of the kinase inhibitory protein (KIP) family. It interacts with and inhibits different CDK complexes (e.g., cyclin B/CDK1, cyclin A/CDK2, and cyclin D/CDK4) to arrest the cell cycle. Several cyclin/CDK complexes are potential upstream regulators of the kinase for eukaryotic elongation factor 2 (eEF2K), which phosphorylates eEF2 and results in repression of general protein synthesis. Substantial evidence has demonstrated that protein synthesis is required for long-term forms of synaptic plasticity and memory. We intend to investigate the neuronal effects of p27 using a transgenic mouse model with p27 conditionally suppressed in neurons. We performed a series of behavioral tests including open field (OF), novel object recognition (NOR) task, Morris water maze (MWM) to assess cognitive function in both the heterozygous p27 knock down and homozygous p27 knock out mice aging between 3-6 months. The results indicate that cognitive function is normal (compared to the wild type littermates) in the adult mutant mice with suppression of p27. We next will examine potential aging-related effects with genetic suppression of p27.

Disclosures: J.V. Patel: None. **X. Wang:** None. **X. Zhou:** None. **T. Ma:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.21/WW50

Topic: H.08. Learning and Memory

Support: AFOSR LRIR#20RHCOR04

Title: Intensity dependent effects of transcranial direct current stimulation on memory performance and hippocampal protein abundance

Authors: *C. HATCHER-SOLIS[1], J. MARTIN[1], S. HARSHMAN[1], S. H. JUNG[2];
[1]Air Force Res. Lab., Wright-Patterson AFB, OH; [2]Infoscitex, Dayton, OH

Abstract: Transcranial direct current stimulation (tDCS) enhances cognitive performance and neuroplasticity, but its underlying mechanisms in the brain are still unclear. The purpose of this study was to investigate the effects of tDCS stimulation intensity on memory performance and examine the associated changes in hippocampal protein abundance. Two different current intensities (250 µA and 500 µA) of anodal tDCS were applied to Sprague-Dawley rats (male, 8-10 weeks old) for 30 min before training and 24 hours later before testing during the passive avoidance test (PAT). Memory performance measured by the PAT was enhanced by both current intensities. To investigate the underlying mechanisms for enhanced performance, hippocampal synaptosomes were isolated and profiled using Waters Acquity Ultra Performance Liquid Chromatography for bottom-up proteomics. Normalized proteomic abundance datasets were analyzed by multiple bioinformatics methods and advanced statistical analyses. Analysis of protein-protein interaction-related functions and pathways indicated that hippocampal synaptosomes were significantly modified by anodal tDCS at 250 µA and 500 µA. Based on the results of bioinformatics and network analyses, both current intensities enhanced glutamatergic and dopaminergic synapse pathways in addition to long-term potentiation (LTP) pathways in the hippocampus. However, a greater number of tDCS-induced modifications were detected after anodal tDCS at 250 µA including enhanced metabolic pathways, GABAergic and cholinergic synapse pathways. In conclusion, we report that although anodal tDCS at 250 µA and 500 µA both enhance memory performance, the underlying mechanisms may be different based on the pathways that were found to be significantly upregulated. Our findings have important implications for understanding the dose-dependent effects of tDCS and determining the optimal parameters for therapeutic applications. This study was completed under an approved IACUC protocol.

Disclosures: C. Hatcher-Solis: None. **J. Martin:** None. **S. Harshman:** None. **S.H. Jung:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.22/WW51

Topic: H.08. Learning and Memory

Support: NIMH F31MH126576
NIH T32-NS105607

Title: Histone variant H2BE promotes chromatin accessibility, synaptic function, and long-term memory

Authors: *E. R. HYATT[1], S. LOUZON[2], K. PALOZOLA[3], Q. QIU[4], K. CHOI[5], N. PRESCOTT[7], Y. DAVID[7], M. V. FUCCILLO[4], H. WU[4], E. KORB[6];
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Abstract: In the central nervous system, histone variants are critical for the precise control of neuronal gene expression and proper cognitive function. The histone variant H2BE was discovered in the mouse olfactory epithelium, where it affects olfactory neuron function and longevity. While H2BE was previously thought to be exclusively expressed in the olfactory system, our lab developed a highly specific antibody against H2BE and demonstrated that H2BE is present throughout the brain. However, despite the importance of histone variants in controlling neuronal function, to date, H2BE remains unstudied outside of the olfactory system. Using CUT&Tag-sequencing, we found that H2BE is specifically enriched at promoters in mouse cortical neurons. In addition, H2BE promotes open chromatin and is required for proper expression of synaptic genes and synaptic function. Lastly, we found that H2BE is critical for learning and long-term memory formation in young adult mice. This work contributes to our understanding of how neurons use chromatin to translate diverse environmental signals into a transcriptional profile that supports long-lasting memories and adaptive behavioral responses.

Disclosures: E.R. Hyatt: None. **S. Louzon:** None. **K. Palozola:** None. **Q. Qiu:** None. **K. Choi:** None. **N. Prescott:** None. **Y. David:** None. **M.V. Fuccillo:** None. **H. Wu:** None. **E. Korb:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.23/WW52

Topic: H.08. Learning and Memory

Support: AFOSR Grant 14RH08COR

Title: Comparison of acute transcranial direct current stimulation effects on different brain regions

Authors: *S. H. JUNG[1], C. HATCHER-SOLIS[2];
[1]Cognitive Enhancement and Biodynamics Br., [2]Commander's Action Group, U.S. Air Force Res. Lab., Wright-Patterson Air Force Base, OH

Abstract: Accumulating evidence indicates that transcranial direct current stimulation (tDCS) affects cognition in a region specific and intensity-dependent manner. Our research group has provided some underlying molecular mechanisms by which tDCS enhances memory and learning. However, it is still needed to elucidate how tDCS modifies molecular regulation in the brain, especially in different regions with different intensities and polarities. Here, we examined the proteomics regulation in synaptic regions of different brain regions after one-time cathodal and anodal tDCS. One session of cathodal/anodal tDCS was applied to Sprague Dawley rats (male, 8-10 weeks old) for 30 minutes near bregma 0-5 mm at the current intensity of shame (0), 250 or 500uA. In 2-hour post-tDCS, different brain regions were collected in post 2 hours (n = 5/group). The brain regions we analyzed include cortex (the cognitive brain region and the nearest brain region from the stimulating electrode), hippocampus (memory & learning regions), and cerebellum (the farthest brain region from the stimulating electrode). Synaptoneurosomes were isolated and profiled by LC-MS/MS mass spectrometry. With a target false discovery rate of 0.05, proteomic data was determined, normalized, and analyzed. Different analytics methods, such as, clustering analysis, principal components analysis, classification analysis, functional enrichment analysis, protein-protein interaction analysis, Ingenuity pathway analysis, etc., were conducted to analyze the synaptoneurosomes data from different brain regions. Our data shows both brain region-specific and similar effects. Additionally, tDCS intensity and polarity dependent changes were also detected. Thus, our complicated data suggest that acute one-time tDCS affects regulations of synaptoneurosomes in different brain regions. Additionally, because we only present here the data collected from our project for which acute one-time stimulation was applied and tissues were collected after 2 hours, future studies should be designed to investigate different application of tDCS and exclude some limitations our study had.

Disclosures: S.H. Jung: None. **C. Hatcher-Solis:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.24/WW53

Topic: H.08. Learning and Memory

Support: Simons Collaboration on Plasticity in the Aging Brain
Lev Mikheev
NIH F32 AG079490
NIH F32 AG081038
NSF Pre-doctoral award
NIA R01 AG077816
NIH Director's Pioneer Award DP1AG077430

Title: EGL-30/GNAQ activation rejuvenates memory in two-year-old mice

Authors: *M. E. STEVENSON[1], G. BIERI[2], R. KALETSKY[1], J. M. ST. ANGE[1], L. REMESAL[2], K. J. B. PRATT[2], S. ZHOU[1], Y. WENG[1], S. A. VILLEDA[2], C. MURPHY[1]; [1]Princeton Univ., Princeton, NJ; [2]Anat., Univ. of California San Francisco (UCSF), San Francisco, CA

Abstract: Age-related cognitive decline is debilitating. Memory decline with age has been identified across species, from worms to humans. We first found that the expression of gain-of-function Gαq/*egl-30* restores long-term associative memory in aged worms experiencing memory loss. EGL-30/GNAQ and Gαq signaling pathways are highly conserved between worms and mammals, so we wondered whether this pathway also has a role in mammalian cognitive decline. We found that GNAQ is enriched in excitatory neurons in the mouse hippocampus, and its expression declines with age. Next, we tested whether expression of GNAQ gain-of-function could improve memory in aged mice. When expressed in hippocampal neurons of 24-month-old mice, GNAQ gain-of-function significantly improved long-term memory performance. This demonstrates that the molecular and genetic pathways between *C. elegans* and other mammals are highly conserved, as increased GNAQ function is sufficient to rescue memory in two-year-old mice. Single-nucleus RNAseq showed cell autonomous and cell non-autonomous changes in genes related to synaptic structure and function, axon guidance, and pathways involved in learning and memory. We then tested worm orthologs of mouse genes upregulated by GNAQ(gof) overexpression for functional roles in EGL-30/GNAQ-dependent enhancement of worm memory. Several genes were found to be critical for improved memory. These findings demonstrate that EGL-30/GNAQ is a conserved regulator of cognitive decline and has therapeutic potential in the treatment of cognitive aging.

Disclosures: M.E. Stevenson: None. **G. Bieri:** None. **R. Kaletsky:** None. **J.M. St. Ange:** None. **L. Remesal:** None. **K.J.B. Pratt:** None. **S. Zhou:** None. **Y. Weng:** None. **S.A. Villeda:** None. **C. Murphy:** None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.25/WW54

Topic: H.08. Learning and Memory

Support: ISN Grant CAEN-1B

Title: Regulation of immediate-early genes by curcumin in scopolamine-induced amnesic mice

Authors: *A. GAUTAM;
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Abstract: Several research studies have revealed curcumin's anticarcinogenic, antioxidant, and immunomodulatory properties. However, definite evidence on the molecular pathways triggered by curcumin against neurological disorders, particularly amnesia or memory loss, is unavailable. As the memory process involves an interaction of diverse synaptic plasticity genes (SPGs), we hypothesize that curcumin regulates the expression of these genes in brain areas linked with memory processing. To test this hypothesis, we looked at how curcumin affected behaviour and the expression of four SPGs (Arc, FMRP, c-fos and zif-268) in scopolamine-induced amnesic male mice. The Morris Water Maze test was administered for a week to assess their behavioural changes. Real-time PCR wand was used to examine the mRNA levels, whereas Western blotting was used to examine protein levels of SPGs in the hippocampus and prefrontal cortex. In both brain areas, we found a substantial downregulation of immediate-early genes (IEGs) during scopolamine-induced amnesia, which was upregulated by pre- and post-curcumin treatment. Surprisingly, we did not observe any significant change in the levels of other SPGs, i.e. non-IEGs. Our research indicates a molecular pattern for how curcumin alleviates amnesia, but more research on upstream signalling pathways would support the extract's medical utility in memory issues.

Disclosures: A. Gautam: None.

Poster

PSTR306. Genes and Molecular Mechanisms of Learning and Memory I

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR306.26/WW55

Topic: H.08. Learning and Memory

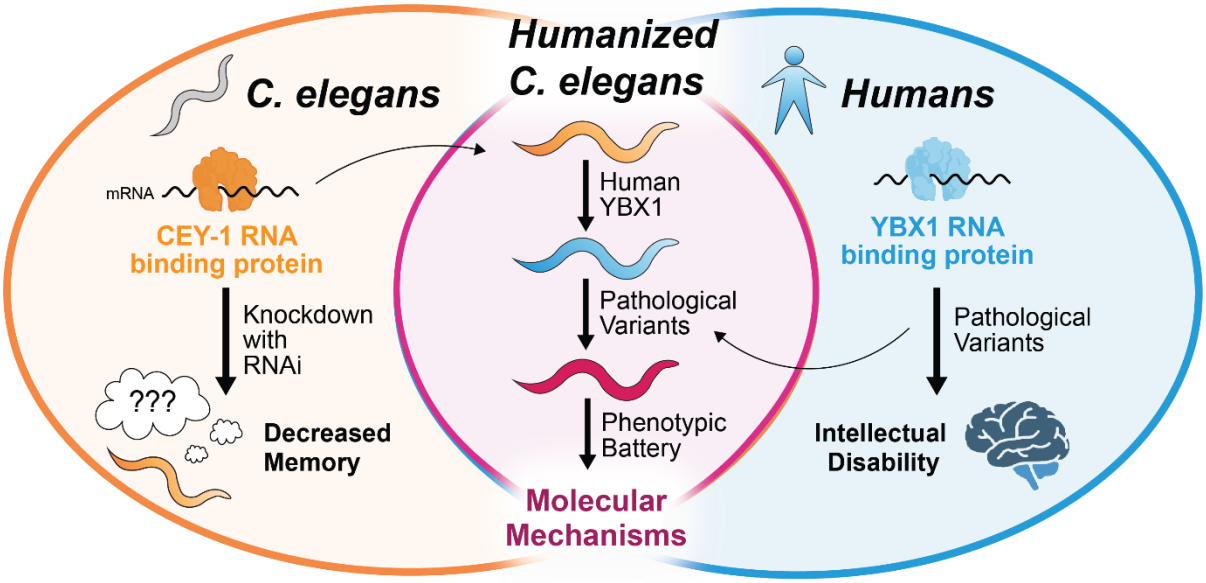
Support: F31 NS129312-01
DP2 NS132372

Title: Cey/ybx rna binding proteins regulate associative memory in c. elegans and play a previously unappreciated role in human cognitive health

Authors: *A. HAYDEN[1], K. BRANDEL[1], P. MERLAU[2], E. PIETRYK[3], R. AREY[2];
[1]Neurosci., [2]Mol. and Cell. Biol., [3]Genet., Baylor Col. of Med., Houston, TX

Abstract: RNA binding proteins regulate RNA metabolism, including the translation of target mRNAs. Translational control of mRNAs is especially important in the nervous system, as novel protein synthesis is necessary for cognition. However, despite their biological significance, many RNA binding proteins within the nervous system remain uncharacterized in cognition. We sought to determine the role of a conserved family of RNA binding proteins, the CEY/YBX RNA binding proteins, in cognitive health. We first identified that of the four CEY RNA binding proteins in *C. elegans,* CEY-1 is the primary ortholog to mammalian YBX's. We then determined that both truncated CEY-1 with a functional RNA binding domain and full loss of CEY-1 cause learning and associative memory deficits using positive associative olfactory

assays. To identify if this was due to a tissue-autonomous role of CEY-1 in the adult nervous system, we next tested whether adult-only, neuron-specific knockdown of CEY-1 using RNAi decreased associative memory. We identified neuronal CEY-1 as a regulator associative memory in adult *C. elegans*. To determine whether mammalian YBX RNA binding proteins are equally important for cognition, we next examined whether dysfunction of human YBX1, YBX2, and/or YBX3 are associated with neuronal symptoms. Using publicly available and institute-specific human variant datasets, we found that over 80% of patients with single nucleotide variants in any YBX RNA binding protein have severe neurological symptoms. Importantly, the most common symptom is intellectual disability, mirroring our findings in *C. elegans*. In summary, we found a new role for the CEY/YBX RNA-binding proteins in memory and cognition. In ongoing work, we are investigating the mechanisms of specific human variants using humanized *C. elegans* and what pathways are altered when CEY/YBX function is disrupted. These studies suggest that mechanisms in *C. elegans* can inform the molecular underpinnings of YBX-related neurological symptoms in human patients and underscore the importance of neuronal RNA binding proteins in cognition.



Disclosures: **A. Hayden:** None. **K. Brandel:** None. **P. Merlau:** None. **E. Pietryk:** None. **R. Arey:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.01/WW56

Topic: H.12. Aging and Development

Support: CIHR
BrainSCAN

Title: Examining sex-differences in cognitive impairment in patients with Parkinson's disease

Authors: *K. PATEL[1], K. VAN HEDGER[1], S. PASTERNAK[1], M. MASELLIS[2], R. CAMICIOLI[3], O. MONCHI[4], P. MACDONALD[1];
[1]Univ. of Western Ontario, London, ON, Canada; [2]Univ. of Toronto, Toronto, ON, Canada; [3]Univ. of Alberta, Edmonton, AB, Canada; [4]Univ. de Montreal, Montreal, QC, Canada

Abstract: Parkinson's disease (PD) is one of the fastest growing age-related, progressive, neurodegenerative disorders. Cognitive impairment, progressing to dementia, is the most common non-motor symptom of PD and can be debilitating to one's quality of life. Previous studies report sex-specific differences in cognitive impairment in patients with PD, with males having a greater prevalence and progression of cognitive impairment compared to females. However, there remains a need to further investigate these findings in larger samples with greater variability in age and disease duration. We gathered data from a large cohort (n=430, 117 female) of patients with PD who completed the Montreal Cognitive Assessment (MoCA) and self-reported biological sex, age, and disease duration. Participants had an average age of 69.50 (SD = 6.92), an average disease duration of 6.41 years (SD = 3.97) with no significant differences between males and females in age ($t(428) = -1.10$, $p = .27$) and disease duration ($t(428) = -.16$, $p = .87$). We used linear regression to investigate sex-specific differences in MoCA total score and found that sex significantly predicted MoCA total score after controlling for age and disease duration, $B = -1.44$, $t(426) = -3.66$, $p < .001$, $R^2 = .17$, $F(3, 426) = 29.44$, $p < .001$, with males having lower MoCA scores than females. MoCA total scores ranged from 5.00 to 30.00. Our results show sex-specific differences in cognitive impairment in patients with PD, as measured by the MoCA, after controlling for age and disease duration. In this large and varied sample of PD patients, we support previous findings that sex impacts the development of cognitive impairment in PD. Follow up analyses will investigate potential sex differences in specific cognitive domains, as measured by the MoCA sub-scales and other cognitive tests. Additionally, we are examining associations between cognitive impairment and brain structure using diffusion MRI. Overall, this study will provide a better understanding of how sex differences affect the cognitive profile of PD.

Disclosures: K. Patel: None. **K. Van Hedger:** None. **S. Pasternak:** None. **M. Masellis:** None. **R. Camicioli:** None. **O. Monchi:** None. **P. MacDonald:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.02/WW57

Topic: H.12. Aging and Development

Title: Does Alzheimer's disease have a linear negative effect on thinking and emotion? From the six years of observation in the home environment

Authors: *A. ONZO[1], K. MOGI[2], Y. TATEWAKI[3], B. THYREAU[4], Y. TAKI[5];
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Abstract: Studies based on continuous and intimate observations of people with Alzheimer's disease can provide unique insights. Here we report the observation of six-year longitudinal changes after the initial diagnosis of AD in gray matter thickness from MRI images of the whole brain of the mother (KO) of the first author (AO) now with severe AD. The rate of accumulation of amyloid-beta and/or tau varies from region to region, and it is known that the primary sensory areas and primary motor cortex and the subcortical areas remain comparatively intact even many years after the initial diagnosis (Braak & Braak, 1991). It is also known that those remaining brain functions sometimes enable them to have lucid moments (Edvardsson, et al. 2008). If some conditions are met, such as having someone compensate for the abilities that they lost, or being in a secure environment, they may behave like the person they have always been, just as in the anecdotal BBC report of the case of Marta Gonzalez, a former ballet dancer. MG started dancing as she once did the moment the music came on, even after experiencing difficulty in verbal communication. Here we compared the six-year longitudinal changes after the initial diagnosis of AD in gray matter thickness from MRI images of the whole brain of KO (born 1950, 65 years old at the time of diagnosis) with severe AD, with longitudinal data from 45 non-demented people possessed by Tohoku University. KO showed changes typical of people with AD, with the medial prefrontal cortex and the temporoparietal junction atrophying exceptionally fast compared with non-demented people. KO has indeed difficulty in making and remembering autobiographical memories. However, surprisingly, compared with the non-demented, the speed of atrophy in the dorsolateral prefrontal cortex, which is said to correlate with IQ (Duncan, et al. 2000), and in the orbitofrontal cortex, which is involved in complex emotions such as regret and guilt (Camille, et al. 2004), were not exceptional. Moreover, the right Heschl's gyrus, which is related to pitch discrimination (Bermudez et al, 2009), atrophied exceptionally slowly even compared with the non-demented. It might reflect KO's 45 years of piano teaching and her remaining sensitivity to sound. It is as important for families to know what abilities remain as well as to know what abilities have been damaged. We will discuss changes in the brain and personality based on the six-year observation by the family member AO who has lived with KO. Our report would suggest a way to explore the remaining capabilities of individuals from information on longitudinal changes in regional cortical gray matter volumes (Thyreau & Taki, 2020).

Disclosures: A. Onzo: None. **K. Mogi:** None. **Y. Tatewaki:** None. **B. Thyreau:** None. **Y. Taki:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.03/WW58

Topic: H.12. Aging and Development

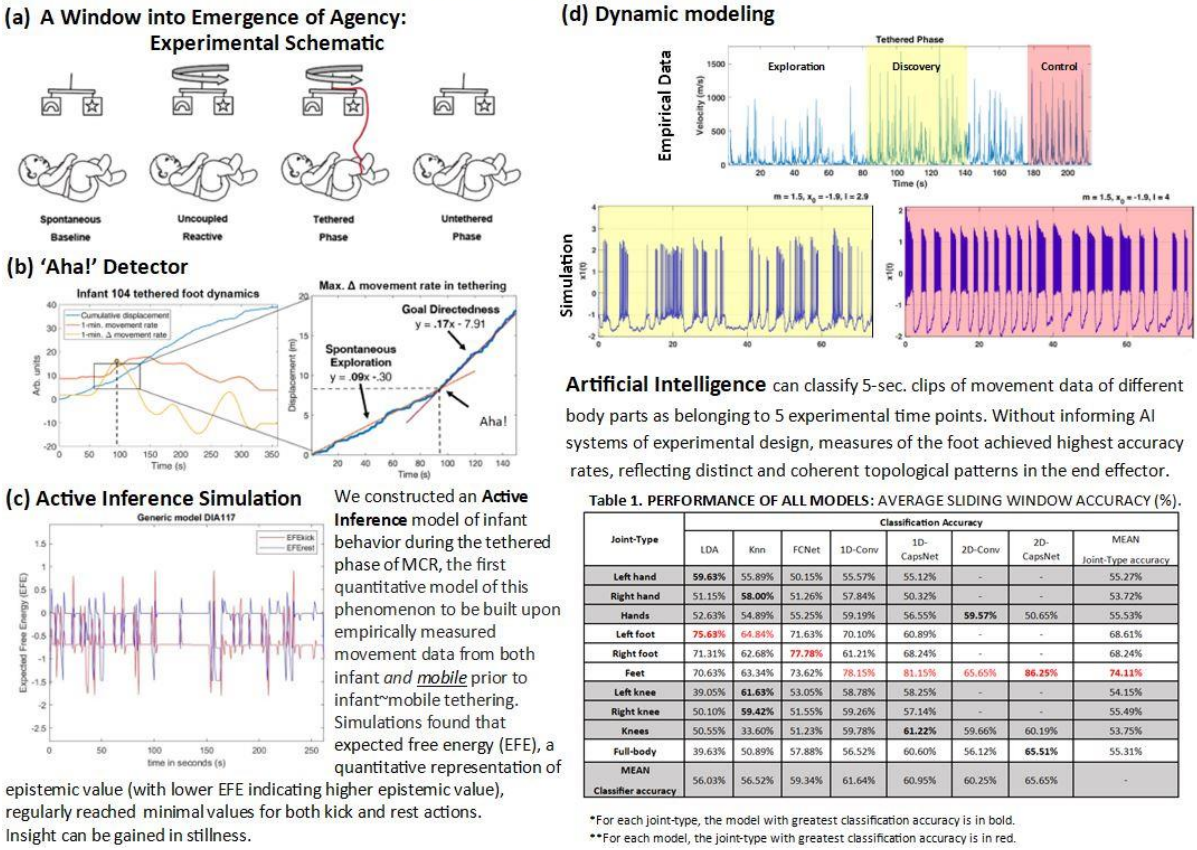
Support: J.A.S.K. and A.T.S. supported by the FAU Foundation (Eminent Scholar in Science).
D.C. and M.K. supported by UKRI Turing AI Fellowship 2021-2025 funded by the EPSRC (grant number EP/V025724/1)
M.K. supported by a Vice Chancellor's Research Scholarship

Title: Coordination Dynamics Meets Active Inference and Artificial Intelligence (CD + AI^2): A multi-pronged approach to understanding the dynamics of brain and the emergence of conscious agency

Authors: *A. T. SLOAN[1], N. A. JONES[1], N. BOITEN[2,3], K. J. FRISTON[3], M. KHODADADZADEH[4,5], D. COYLE[4,5], K. GUDIBANDA[6], V. K. JIRSA[6], J. A. S. KELSO[1,4]; [1]Ctr. for Complex Systems & Brain Sci., Florida Atlantic Univ., Boca Raton, FL; [2]Interdisciplinary Studies, Univ. of Amsterdam, Amsterdam, Netherlands; [3]Wellcome Trust Ctr. for Neuroimaging, Univ. Col. London, London, United Kingdom; [4]Intelligent Systems Res. Ctr., Ulster Univ., Ulster, United Kingdom; [5]Bath Inst. for the Augmented Human, Bath, United Kingdom; [6]Inst. de Neurosciences des Systèmes, Aix Marseille Univ., Marseille, France

Abstract: How do humans discover their ability to act on the world? By tethering a baby's foot to a mobile (Fig. 1a) and measuring the motion of both in 3D, we explore how babies begin to make sense of their coordinative relationship with the world and realize their ability to make things happen (*N*= 16; mean age = 100.33 days). Machine and deep learning classification architectures (*e.g.*, CapsNet) indicate that functionally connecting infants to a mobile via a tether influences the baby movement most where it matters, namely at the point of infant~world connection (Table 1). Using dynamics as a guide, we have developed tools to identify the moment an infant switches from spontaneous to intentional action (Fig. 1b). Preliminary coordination dynamics analysis and active inference generative modeling indicate that moments of stillness hold important epistemic value for young infants discovering their ability to change the world around them (Fig. 1c). Finally, a model of slow~fast brain coordination dynamics based on a 3D extension of the Jirsa-Kelso Excitator successfully simulated the evolution of tethered foot activity as infants transition from spontaneous to ordered action. By tuning a small number of parameters, this model captures patterns of emergent goal-directed action (Fig. 1d). Meshing concepts, methods and tools of **A**ctive **I**nference, **A**rtificial **I**ntelligence and **C**oordination **D**ynamics at multiple levels of description, the **CD + AI^2** program of research aims to identify key control parameters that shift the infant system from spontaneous to intentional behavior. The potent combination of mathematical modeling and quantitative analysis along with empirical study allow us to express the emergence of agency in quantifiable, lawful terms.

Fig. 1. The CD + AI^2 Approach



Artificial Intelligence can classify 5-sec. clips of movement data of different body parts as belonging to 5 experimental time points. Without informing AI systems of experimental design, measures of the foot achieved highest accuracy rates, reflecting distinct and coherent topological patterns in the end effector.

We constructed an **Active Inference** model of infant behavior during the tethered phase of MCR, the first quantitative model of this phenomenon to be built upon empirically measured movement data from both infant *and* mobile prior to infant~mobile tethering. Simulations found that expected free energy (EFE), a quantitative representation of epistemic value (with lower EFE indicating higher epistemic value), regularly reached minimal values for both kick and rest actions. Insight can be gained in stillness.

Table 1. PERFORMANCE OF ALL MODELS: AVERAGE SLIDING WINDOW ACCURACY (%).

Joint-Type	Classification Accuracy							
	LDA	Knn	FCNet	1D-Conv	1D-CapsNet	2D-Conv	2D-CapsNet	MEAN Joint-Type accuracy
Left hand	**59.63%**	55.89%	50.15%	55.57%	55.12%	-	-	55.27%
Right hand	51.15%	**58.00%**	51.26%	57.84%	50.32%	-	-	53.72%
Hands	52.63%	54.89%	55.25%	59.19%	56.55%	**59.57%**	50.65%	55.53%
Left foot	**75.63%**	64.84%	71.63%	70.10%	60.89%	-	-	68.61%
Right foot	71.31%	62.68%	**77.78%**	61.21%	68.24%	-	-	68.24%
Feet	70.63%	63.34%	73.62%	78.15%	81.15%	65.65%	**86.25%**	**74.11%**
Left knee	39.05%	**61.63%**	53.05%	58.78%	58.25%	-	-	54.15%
Right knee	50.10%	**59.42%**	51.55%	59.26%	57.14%	-	-	55.49%
Knees	50.55%	33.60%	51.23%	59.78%	**61.22%**	59.66%	60.19%	53.75%
Full-body	39.63%	50.89%	57.88%	56.52%	60.60%	56.12%	**65.51%**	55.31%
MEAN Classifier accuracy	56.03%	56.52%	59.34%	61.64%	60.95%	60.25%	65.65%	-

*For each joint-type, the model with greatest classification accuracy is in bold.
**For each model, the joint-type with greatest classification accuracy is in red.

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Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.04/WW59

Topic: H.12. Aging and Development

Support: NIH-NIA Grant AGO06265

Title: Examining Differences in Amyloid and White Matter Hyperintensity in Older Adults with Distinct Cognitive Profiles

Authors: *S. MONIER[1,2], E. SMITH[2], J. P. HENNESSEE[2], J. BACCI[2], D. PARK[2];
[1]Univ. of Texas at Dallas-Center for Vital Longevity, Richardson, TX; [2]Univ. of Texas at Dallas, Dallas, TX

Abstract: While cognitive decline is commonly observed with age, there is significant individual variability. Additional research is needed to examine whether cognitively-normal (CN) older adults with diverse aging profiles also vary in Alzheimer's Disease (AD) pathology. We investigated differences in baseline amyloid (Aβ) among older adults with distinct cognitive profiles, characterized by initial memory performance and decline trajectory. Presence of white matter hyperintensities (WMH), believed to be associated with age-related cognitive decline, was also assessed. A total of 169 CN participants (ages 60-89; 61.5% F) with two time-points of cognitive data were included. Episodic memory (EM) was assessed using a composite score from multiple cognitive batteries and change was annualized. Participants underwent PET imaging with radiotracer AV-45 18F-Florbetapir to evaluate cortical Aβ levels. Mean cortical SUVR was computed across 8 cortical ROIs, normalized to cerebellar gray matter. Structural MRI was conducted and baseline global WMH levels were assessed. Group membership was based on baseline EM scores and the decline rates throughout study duration. To ensure sufficient statistical power, only groups of over 10 participants were included in subsequent analyses, leaving 4 groups: 1) participants with average baseline EM and decline rate (*Average-Normative,* N = 68); 2) those with average baseline EM and a decline rate greater than one SD above sample average (*Average-Accelerated*, N = 16)*;* 3) participants with below baseline EM and an average decline rate (*Low-Normative,* N = 13); 4) participants at one SD above the average EM and an average decline rate (*High-Normative*, N = 21). Analysis of variance controlling for age, sex, and education revealed group differences in baseline global Aβ (p = .002), with the *Average-Accelerated* group showing higher levels than both *Average-Normative* and *Low-Normative* groups. Cortical regions demonstrating this relationship included the precuneus (p < .001), lateral parietal (p = .002), and the posterior cingulate (p = .001), known as early Aβ accumulating regions. Baseline WMH also differed among groups (p = .029), with *Average-Accelerated* exhibiting higher levels than the *Average-Normative* group (p = .049). The results of this study suggest that baseline Aβ and WMH may serve as biomarkers for identifying older adults with distinct cognitive profiles and decline trajectories. These findings emphasize the importance of considering both baseline cognition and decline trajectories in assessing AD-related pathology to gain a broader understanding of risk factors associated with cognitive decline in older adults.

Disclosures: S. Monier: None. **E. Smith:** None. **J.P. Hennessee:** None. **J. Bacci:** None. **D. Park:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.05/WW60

Topic: H.12. Aging and Development

Title: Neurocognitive substrates of age-related impairment in search and foraging behaviours

Authors: *S. K. SALO[1,2], M. E. ROSER[1,2], A. D. SMITH[1,2];
[1]Sch. of Psychology, [2]Brain Res. and Imaging Ctr., Univ. of Plymouth, Plymouth, United Kingdom

Abstract: A prominent theory proposes that human cognitive control processes have their roots in foraging behaviour. This has been explored using simple 2D desktop tasks, and findings reveal that cognitive ageing may be revealed through inefficiencies in search behaviours before it is evident in other domains. However, whilst desktop tasks are generally considered to be simple and controlled models for naturalistic foraging, they lack key components that contribute to real-world behaviours, including the requirement to explore larger-scale environments and the integration of spatial reference frames. Since some visual search phenomena do not appear to transfer to large-scale search, it is important to ascertain how ageing affects foraging behaviour when it is enacted in a more authentic context. In addition, a finer grain of insight can be gained from relating change in the optimality of search behaviour to the cognitive and neural underpinnings of these behaviours. In the present study, younger (18-35 years) and older (>65 years) adults engaged in a simple foraging task in an immersive virtual environment. Participants were presented with multiple tables, each bearing a display of containers that were distinguished either by a single feature (colour) or a conjunction of features (colour and shape). Participants were required to search beneath each container for a target object (a ball) and to collect as many targets as possible within 60s. Participants also completed a battery of cognitive assessments, measuring executive function, spatial working memory, verbal and visual memory, reaction time, and rate maximisation. Finally, diffusion weighted imaging was employed to provide estimates of connectivity in frontal cortices.Analyses revealed that structural markers of ageing (fractional anisotropy and mean diffusivity) were predictive of decline in spatial working memory, visual learning, and executive function. Older adults displayed relative inefficiencies in their foraging decisions, both in the 2D rate maximisation task and in the 3D foraging task – their search was less organised, they collected fewer targets, and they displayed a tendency to exploit rather than explore. Together, these findings provide a more comprehensive account of the relationship between environmental search and its neurocognitive underpinnings. Further exploration of the relationship between neurodegenerative signatures and control processes will not only help to elucidate a major theory of human cognition but may also improve our abilities to provide early detection of atypical ageing in neurodegenerative conditions.

Disclosures: S.K. Salo: None. **M.E. Roser:** None. **A.D. Smith:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.06/WW61

Topic: H.12. Aging and Development

Title: Improvement of lifestyle and cognitive function through quantifying brain health

Authors: *K. KOKUBUN[1], Y. TOYAMA[2], M. OKAMOTO[1], Y. YAMAKAWA[1,3,4,5];
[1]Kyoto Univ., Kyoto, Japan; [2]bspr co., ltd., Shibuya, Tokyo, Japan; [3]Tokyo Inst. of Technol., Meguro, Tokyo, Japan; [4]Brain Impact, Kyoto, Japan; [5]Kobe Univ., Kobe, Japan

Abstract: In this study, the Brain Healthcare Quotient (BHQ: Brain Healthcare Quotient) (Nemoto et al., 2017), an index that quantifies brain health from MRI images, was used to evaluate whether it can promote good lifestyle habits for brain health in people. Participants were asked to use an app that promotes brain training and a healthy lifestyle. All participants were offered free access to the 'Estimated BHQ' function that enabled them to estimate their BHQ from the app's activities. In addition, Participants who actively used the app were provided with MRI BHQ measurements. Before and after using the app, participants were asked to answer a voluntary questionnaire on their motivation for participating, their medical history, lifestyle habits, and cognitive function test. 256 people participated in the study, 147 completed the questionnaire before using the app and 51 completed the questionnaire after using the app. The most common motivation for participation was “quantifying brain health seemed interesting”. 49% of the participants had a chronic disease, which was higher than the national statistic of 39.6% (White Paper on Health and Labour, 2014). An analysis of variance was conducted on nutritional intake and physical activity, with the presence or absence of chronic diseases and intervention timing as factors. The results showed a main effect of intervention timing for 'nutrition' ($p = 0.04$) and the interaction was significant ($p = 0.02$). A simple main effect was found that only the group with chronic diseases had significantly higher scores after using the app ($p = 0.01$). For 'low-intensity exercise', a main effect was found for both presence of chronic disease and intervention timing ($p = 0.03$, $p = 0.02$), and the interaction tended to be significant ($p = 0.08$). A simple main effect showed a significant increase in physical activity after using the app in the group with chronic disease ($p = 0.04$). Cognitive function test scores also increased after using the app, regardless of the presence or absence of chronic disease ($p = 0.04$). Based on the results of this study, it is assumed that people with chronic diseases actively participated in using the 'quantification of brain health status' as an incentive. Furthermore, people with chronic diseases may be more likely to improve their lifestyle through the brain healthcare app. Although the results of cognitive function tests are not able to remove learning effects, several studies have shown a relationship between diet and exercise and cognitive function (e.g., Titova OE et al., 2013; Colcombe SJ, et al., 2006). Hence, it is suggested that improving those habits in the participants with chronic disease may improve cognitive function.

Disclosures: **K. Kokubun:** A. Employment/Salary (full or part-time):; bspr corp. **Y. Toyama:** A. Employment/Salary (full or part-time):; bspr corp. **M. Okamoto:** A. Employment/Salary (full or part-time):; BHQ Corp. **Y. Yamakawa:** A. Employment/Salary (full or part-time):; BHQ Corp.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.07/WW62

Topic: H.12. Aging and Development

Support: NIA Grant P01AG009973
The Phyllis F. Albstein Fund

Title: Neuronal Pentraxin 2 is a conserved biomarker of cognitive health in aging

Authors: *A. BRANCH[1,2,3,4], R. P. HABERMAN[2,6], A. E. DELGADO[5], S. JI[5], M. XIAO[7], P. F. WORLEY[5], M. GALLAGHER[2,5,4];
[2]Psychological and Brain Sci., [3]Zanvyl Krieger Mind Brain Inst., [4]Kavli Neurosci. Discovery Inst., [5]The Solomon H Snyder Dept. of Neurosci., [1]Johns Hopkins Univ., Baltimore, MD; [6]Biol. Dept., Mary Baldwin Univ., Staunton, VA; [7]The Solomon H Snyder Dept. of Neurosci., JHMI, Baltimore, MD

Abstract: Cognitive decline is a common although not inevitable feature of aging. Identification of protective and exacerbating factors in the aging human brain is confounded by the presence of comorbidities, such as Alzheimer's pathology and cardiovascular disease, as well as the wide range of individual decline profiles. The cognitive aging field needs improved biomarkers which can be modeled in animals to identify and track the progression of age-related cognitive decline separate from pathological factors. Here we provide evidence that neuronal pentraxin 2 (NPTX2), an immediate early gene which mediates activity dependent homeostatic plasticity important for memory function, is a molecular marker of age-related cognitive decline which translates across species. Use of NPTX2 as a biomarker of cognitive health in an animal model of healthy aging will improve our ability to isolate factors contributing to age related cognitive decline in the otherwise healthy brain.

Disclosures: A. Branch: None. **R.P. Haberman:** None. **A.E. Delgado:** None. **S. Ji:** None. **M. Xiao:** None. **P.F. Worley:** None. **M. Gallagher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AgeneBio Incorporated.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.08/WW63

Topic: C.01. Brain Wellness and Aging

Support: NIH PO1-AG09973

Title: The strength of LEC excitatory inputs into Dentate Gyrus PV-INs correlated with cognitive performance in aged rats

Authors: *C. MORENO NARANJO, D. SEVERIN, M. KOH, J. ZHOU, A. CONTREREAS, P. WORLEY, M. GALLAGHER, A. KIRKWOOD;
Johns Hopkins Univ., Baltimore, MD

Abstract: Aging impairs mental properties, including learning and memory. Recent studies have identified hyperactivity in the medial temporal lobe, particularly in the lateral entorhinal cortex (LEC) and the CA3/DG hippocampal subfields, as a dysfunctional condition common to cognitive impairment in aged rats and humans diagnosed with mild cognitive impairment. Previously we showed a reduction of feedforward inhibition elicited by LEC inputs onto DG granule cells, characterized as the ratio of synaptic excitation and inhibition (E/I ratio) in AI rats. A plausible mechanism to explain the reduction of inhibition recruitment is decreased LEC excitatory input onto DG PV-INs. We tested the possibility the overexpressing NPTXs in LEC neurons could rescue the DG granule cells' feedforward inhibition in AI rats. AI rats with comparable learning indexes were injected bilaterally in LECs with either AAV-CaMKII-NPTX2-SEP or AAV2-CaMKII-GFP as a control. We observed thus NPTX2 overexpression in LEC cells nearly doubles the strength of inhibition recruited by rescuing the E/I ratio in AI rats. By the AAV-DlMx-Td transfection approach to visualize DG-PV-INs. We identified PV-INs using immunofluorescence in slices and action potentials (AP) parameters (high firing frequency and AP half-width). We evaluated presynaptic and postsynaptic modification induced by aging, and we found a reduction of excitatory LEC inputs into dentate PV-INs in AI rats compared to AU rats.

Disclosures: C. Moreno Naranjo: None. **D. Severin:** None. **M. Koh:** None. **J. Zhou:** None. **A. Contrereas:** None. **P. Worley:** None. **M. Gallagher:** None. **A. Kirkwood:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.09/WW64

Topic: H.12. Aging and Development

Title: Deficits in force production during multifinger tasks demarcate cognitive dysfunction.

Authors: *R. G. CARSON[1,2], D. BERDONDINI[1], M. CROSBIE[1], C. MCCONVILLE[2], S. FORBES[2], M. STEWART[2], R. Z. X. CHIU[2];
[1]Trinity Col. Inst. of Neurosci. and Sch. of Psychology, Trinity Col. Dublin, Dublin, Ireland;
[2]Sch. of Psychology, Queen's Univ. Belfast, Belfast, United Kingdom

Abstract: The multifinger force deficit (MFFD) is the decline in (maximum) force generated by each finger as the number of fingers contributing to an action is increased. It is a measure of neural sufficiency that is larger in older persons than in the young, and associates with cognitive status. It was assessed here using a particularly challenging form of grip dynamometry that provides minimal tactile feedback via cutaneous receptors and requires active compensation for

reaction forces. It was hypothesised that these factors would accentuate the demands placed on the CNS and provide a particularly sensitive measure of functional brain integrity and cognitive impairment. Sixty-two volunteers took part in the study (42 females, 20 males; median age 72.5 years; range 65-87). Multifinger finger flexion dynamometry was undertaken using the approach described by Ohtsuki et al. (1981). Cognitive status was assessed using the Montreal Cognitive Assessment (MoCA). Eight neuropsychological evaluations (yielding eleven separate scores) and principal component analysis (PCA) was also used as a dimension reduction method to extract latent components of cognitive function. More than half of the 62 participants were unable to complete the dynamometry task successfully. Individuals who could perform the task were demarcated from those who could not, based on MoCA scores (Logistic regression estimate = 0.03, p = 0.044, 0.001 - 0.068 (95% c.i.)). Among 30 participants who complied with the task requirements, the MFFD (r = -0.51 (p = 0.003, -1 - 0.24 (95% c.i.)) and the rate-of-force (rof) MFFD (r = -0.47 (p = 0.007, -1 - -0.19 (95% c.i.)) were negatively correlated with MoCA scores - those with the highest MoCA scores tended to exhibit the smallest deficits, and vice-versa. It was indicated that only the first two PCs should be retained for further analysis. For the MFFD, there were corresponding associations with both latent components of cognitive function (PC1: r = -0.41 (-1 - -0.12 (95% c.i.), FDR = 0.021); PC2: -0.65 (-1 - -0.43 (95% c.i.), FDR = 0.0005)). To a lesser degree, this was also the case for the rofMFFD (PC1: r = -0.19 (-1 - 0.12 (95% c.i.), FDR = 0.169); PC2: -0.65 (-1 - -0.43 (95% c.i.), FDR = 0.0003)). The results add further weight to the assertion that deficits in force production during multifinger tasks are sensitive to cognitive dysfunction.

Disclosures: R.G. Carson: None. **D. Berdondini:** None. **M. Crosbie:** None. **C. McConville:** None. **S. Forbes:** None. **M. Stewart:** None. **R.Z.X. Chiu:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.10/WW65

Topic: H.12. Aging and Development

Support: NIH-NIA Grant AGO-06265

Title: Aging and depression trajectories on cognition

Authors: *J. R. BACCI[1], J. P. HENNESSEE[1], E. T. SMITH[2], S. MONIER[3], D. C. PARK[4]; [1]Univ. of Texas at Dallas, Richardson, TX; [2]Univ. of Texas at Dallas, Dallas, TX; [3]Univ. of Texas at Dallas-Center for Vital Longevity, Richardson, TX; [4]Ctr. For Vital Longevity, Univ. of Texas At Dallas, Dallas, TX

Abstract: In older adults the cross-sectional association of depression to cognitive impairments is well defined in the literature, but the relationship of depression to longitudinal cognitive declines is inconsistent. In this study, we investigated the relationship of depressive symptoms

with cognitive performance across the lifespan and predicted that the association of depressive symptoms to cognition would become stronger with age. Additionally, given the varying patterns of depressive symptoms across the lifespan, we explored the relationship of longitudinal depressive symptom trajectories to cognitive declines. The present study included 264 cognitively normal participants, aged 20-89, that completed two time-points of cognitive measures and depression questionnaires over an average of 3.92 years. Trajectory group membership was defined by the severity of depressive symptoms at baseline and the pattern of change over the course of the study. Five trajectory groups were identified: 1) participants with no depressive symptoms across the study ("Healthy Control", N = 34); 2) participants with depressive symptoms that emerged at the second time-point ("Emerging", N = 14); 3) participants with moderate baseline depressive symptoms that declined ("Moderate Declining", N = 82); 4) participants with moderate baseline depressive symptoms that increased ("Moderate Increasing", N = 66); 5) participants with moderate baseline depressive symptoms that remained stable ("Moderate Stable", N = 68). Using hierarchical linear regression, we found that baseline depressive symptoms demonstrated a quadratic age trend ($p < .001$), with depressive symptoms peaking in younger adulthood, declining through middle-age, and slightly rebounding at very late-life. A linear regression controlling for age, sex, and education revealed a significant age by baseline depressive symptom interaction on Reasoning ($p = .024$), where higher depressive symptoms had a more detrimental effect on Reasoning in older adults. Linear mixed effects models controlling for age, sex, and education revealed a significant depressive symptom trajectory group by time since baseline interaction on declines in Reasoning ($p = .008$), where only the Moderate Increasing trajectory group exhibited significant declines in Reasoning. This study provides evidence of the differential associations of depressive symptoms to cognition across the lifespan. While baseline depressive symptoms can be indicative of impaired Reasoning abilities in older adults cross-sectionally, trajectories of depressive symptoms over time can be used to predict longitudinal declines in Reasoning across the lifespan.

Disclosures: **J.R. Bacci:** None. **J.P. Hennessee:** None. **E.T. Smith:** None. **S. Monier:** None. **D.C. Park:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.11/WW66

Topic: H.12. Aging and Development

Support: NIEHS, 1 R21 ES027909

Title: Levels of Blood Iron are Positively Related to Levels of Cognitive Performance in Women at the Menopausal Transition

Authors: *A. L. BARNETT, M. J. WENGER, L. K. BOOZARY, S. F. NEWBOLDS;
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Abstract: Iron accumulates in the brain over time, and the amount of iron present in regions including hippocampus, putamen, caudate nucleus has been shown to be related to the deficits in cognition that are associated with aging. However, women have been shown to have lower levels of both serum iron and brain iron, a difference has been attributed to monthly blood loss during the reproductive years. This raises the question of what happens to brain iron levels at the menopausal transition. If higher serum iron levels are associated with higher brain iron levels and therefore increased oxidative stress, it is possible that women who have relatively lower blood iron levels may have an advantage in terms of brain structure and cognition relative to women who have higher blood iron levels. We examined this possibility in a small (n = 27) sample of women who were either in the earliest (n = 8) or latest (n = 19) stages of menopause. Blood measures of iron were obtained as were MRI-derived estimates of brain iron. Levels of sFt were converted to a percentile ranking based on race and age distributions obtained from the National Health and Nutrition Examination Survey (NHANES) data sets. Cognition was assessed using a set of four tasks, including a face-name associative memory task, which is the focus of this report. In this task, women learned to associate a set of faces with both a set of names and a set of occupations. Memory for these associations was measured both immediately and after an approximately 2 hr delay by presenting each studied face with (a) the associated name and a lure and (b) the associated occupation and a lure. Choice accuracy and reaction times (RTs) were measured and were analyzed using repeated-measures analysis of variance. There was an interaction between test type (face/name, face/occupation) and test time (immediate, delayed) for both accuracy and RT, such that performance was worse at the delayed test but only for the face/name associations. Accuracy for the face/name associations was predicted by age and the percentile of the sFt level at both test times, with the relationship with age being negative and the relationship with sFt being positive. RT for the face/name associations at both test times were predicted only by percentile of the sFt level, with the relationship being negative. This suggests that higher rather than lower levels of iron at the menopausal transition were associated with higher levels of cognitive performance. Further analyses of the blood iron levels will be needed to determine if higher levels of sFt are or are not related to the risk of oxidative stress. Funding: NIEHS, 1 R21 ES027909

Disclosures: **A.L. Barnett:** None. **M.J. Wenger:** None. **L.K. Boozary:** None. **S.F. Newbolds:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.12/WW67

Topic: H.12. Aging and Development

Support: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—362321501/Research Training Group (RTG) 2413 SynAGE.

Title: Novelty detection and stimuli discrimination in healthy and pathological ageing

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Abstract: Novelty detection and stimuli discrimination are particularly impaired in individuals with mild cognitive impairment (MCI) (Lagun et al., 2011, Zola et al., 2013, Crutcher et al., 2009) and individuals diagnosed with Alzheimer's disease (AD) (Daffner et al., 2001) and predict the progression from MCI to AD (Zola et al., 2013, Gaynor et al.,2019). Furthermore, memory for objects and scenes has been shown to decline differently (Güsten et al.,2021). In the present study, we investigate differences in novelty detection and stimuli discrimination among healthy (HC), subjective cognitive decline (SCD), MCI, and AD participants and across stimulus domains. Data for this study was collected from the DELCODE clinical trial. The analyses included 78 HC, 48 individuals with SCD, 15 patients with MCI and 7 patients with AD collectively referred to as the pathology (PAT) group. Participants underwent fMRI while performing a memory discrimination task (Berron et al., 2018). fMRI results were analysed on a study-specific template space to account for potential atrophy-related anatomical deviation in the PAT group. A significant main effect of group on “hits-false alarms" rate was found ($F(2)=279.64$, $p<.001$). The group difference was found between HC and both SCD and PAT ($p<0.001$). No effect of the type of object (room or scene) or interaction was found ($p > 0.05$). The analysis of hits and false alarms (FA) separately revealed no significant main effect of group, stimulus type or their interaction ($p > 0.05$) for FA. However, a significant main effect of group was observed for hits ($F(2) = 683.42$, $p<0.001$).The fMRI results for novelty contrast (*first presentation- repetition*) showed that compared to HC, SCD group showed reduced activation in the fusiform gyri ($T=5.08$, $Z_E=4.86$, $p_{unc}<0.001$). Similarly, the PAT group also showed a reduction in the same area ($T=6.67$, $Z_E=6.18$, $p_{unc}<0.001$), as well as bilateral hippocampus ($T=5.77$, $Z_E= 5.47$, $p_{unc}<0.001$) In conclusion, the findings suggest that: (1) the difference in stimuli discrimination in ageing may primarily stem from the ability to accurately recognise previously encountered stimuli, rather than a failure to identify a similar stimulus as new; (2) subjective complaints of memory problems may indeed indicate cognitive decline, despite not be easily detected using traditional diagnostic measures; (3) the reduced fMRI activation observed in the novelty contrast suggests a gradual decline in the task-related activation during the progression from a healthy state to pathology. These results highlight the importance of evaluating stimulus recognition and discrimination in ageing populations.

Disclosures: E. Lancini: None. **D. Berron:** A. Employment/Salary (full or part-time):; scientific cofounder of neotiv GmbH. **E. Düzel:** A. Employment/Salary (full or part-time):; scientific cofounder of neotiv GmbH. **M. Betts:** None. **D. Hämmerer:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.13/WW68

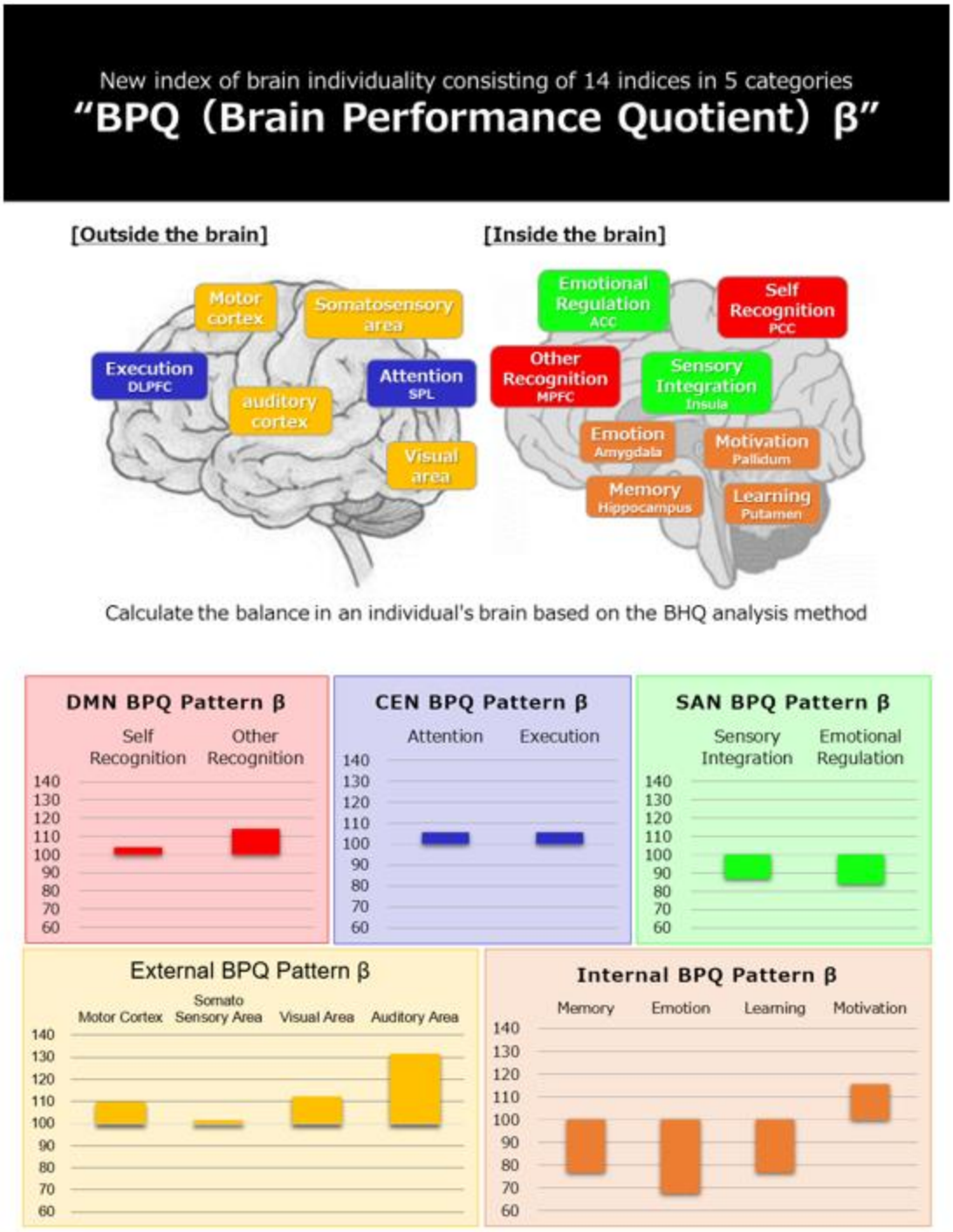
Topic: H.12. Aging and Development

Support: the ImPACT Program of Council for Science, Technology, and Innovation (Cabinet Office, Government of Japan)

Title: Sex and Age Differences in Japanese on Brain Individuality Using MRI

Authors: *Y. YAMAKAWA[1,2,3,4], K. KOKUBUN[1], M. OKAMOTO[1], M. KAWAMORI[2], H. SHIMAZU[2], T. OTSUKA[1], N. FUJII[3], K. TOMITA[3], Y. KOIKE[4], K. NEMOTO[5];
[1]Kyoto Univ., Kyoto, Japan; [2]Brain Impact, Kyoto, Japan; [3]Kobe Univ., Kobe, Japan; [4]Tokyo Institue of Technol., Meguro,Tokyo, Japan; [5]Univ. of Tsukuba, Tsukuba, Japan

Abstract: Brain imaging using MRI has been used mainly by doctors. We have tried to convert brain images into a numerical value that is easy for everyone to understand. We normalized the degree of brain atrophy and named it BHQ (Brain healthcare Quotient) as the brain version of IQ, which was approved as an international standard. In this study, we developed the BHQ to show the individuality of the brain, and examined whether it could beused for education and human resource development in the future. MRI imaging was performed on 291 experimental collaborators (male; 174, female 117 /20-39 years old; 117, 40-49 years old; 77, 50-69 years old; 97). We normalized the values of 90 cerebral regions from the Local BHQs of 116 AAL brain regions obtained during the conversion of MRI images to BHQs. We selected 28 of these regions with relatively well-defined neuroanatomical roles, and used the bilateral averages as a single value. We named it the Brain Performance Quotient (BPQ) and defined it as a pattern of 14 value sthat indicate brain individuality. As a first step in examining whether the BPQ is indicative of individuality, we analyzed differences by sex and age. PCC and MPFC, part of the Default Mode Network, and Insula and ACC, part of the Saliency Network, were significantly larger for young people than for older people. The SPC and PFC, part of the Central Executive Network, were significantly larger in males than in females. The motor cortex was larger in the elderly, and the auditory cortex was larger in females. Hippocampus was larger in females and older adults, Amygdala was larger in females, and Putamen was larger in young adults. There were no differences insomatosensory or visual cortices or Pallidum according to sex or age.The BPQs generated from the BHQ were characteristically different for different genders and ages. This suggests that the BPQ partially shows the characteristics of each attribute due to differences in gender and age roles in Japan. In the future, we would like to clarify the relationship between BPQ and personality, strong subjects, and job performance, premised on ethical considerations.



Disclosures: **Y. Yamakawa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BHQ Corp. **K. Kokubun:** 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.; bspr corp. **M. Okamoto:** 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.; BHQ Corp., bspr corp. **M. Kawamori:** A. Employment/Salary (full or part-time):; BHQ Corp. **H. Shimazu:** A. Employment/Salary (full or part-time):; BHQ Corp. **T. Otsuka:** 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.; bspr corp.. **N. Fujii:** None. **K. Tomita:** None. **Y. Koike:** 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.; BHQ Corp. **K. Nemoto:** 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.; BHQ Corp..

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.14/WW69

Topic: H.12. Aging and Development

Support: Intramural Research Program of the NIA/ NIH

Title: Neurobiology of age-associated changes in social cognition in rats

Authors: *S. DUTTA GUPTA, E. BURNS, J. M. LONG, E. PEREZ, P. R. RAPP; Neurocognitive Aging Section, Lab. of Behavioral Neurosci., Natl. Inst. on Aging, Baltimore, MD

Abstract: Aging is a multifactorial phenomenon that severely affects cognition over time and increases the risk for neurodegenerative disease. In addition, age affects the prioritization of social goals and subsequent preferences for social companions. These social network characteristics are identified as key elements of successful aging. However, it is unclear whether age-dependent deficits in social cognition mainly reflect the disruption of social network activity or are simply secondary to a more general impairment of cognition. In this study, we aimed to establish a better understanding of this fundamental issue using a Long-Evans rat model of neurocognitive aging. Aged rats (25-27 months) were classified as either aged-unimpaired (AU) or aged-impaired (AI) based on their spatial memory performance relative to young adults (Y; 6-8 months; n = 8-16/group). We assessed sociability and social novelty using a three-chambered social interaction test. In the sociability phase, rats from all three groups spent more time interacting with a trapped stranger conspecific versus an inanimate object on the other side of the apparatus. In the social novelty phase, rats chose between a familiar animal (from the sociability trial) and a novel animal. Y and AU rats spent more time interacting with the novel animal (p_Y = 0.01; p_{AU} = 0.02), however, the AI rats failed to show any preference, indicating a social novelty

deficit ($p > 0.99$). Interestingly, we observed marked individual differences in the social novelty index among the AI rats, with a robust effect size of mean difference compared to the Y rats (Cohen's d = 0.88). Rats from all three groups showed a gradual decline in the short (< 6s; curiosity-driven) and long (> 6s; mutual interaction-driven) bouts of social interaction with the novel conspecific along the test time course. However, the AI rats displayed a significant reduction in the long interaction bouts compared to the Y rats ($p = 0.02$) possibly due to a lack of social motivation. Further analysis indicated that social preference and spatial learning are uncorrelated and independent but overlapping cognitive domains affected in aging. To explore the neurobiology of individual differences in social cognition in aging, next, we quantified oxytocin (OXY) immunoreactive neurons in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus, i.e., neuropeptidergic circuitry implicated in social behavior. We observed a lower OXY+ neuronal number in AI relative to Y in the PVN ($p = 0.02$). Together, our findings provide evidence of a successful preclinical model for studying the neurobiology of age-associated decline in socio-cognitive architecture.

Disclosures: S. Dutta Gupta: None. **E. Burns:** None. **J.M. Long:** None. **E. Perez:** None. **P.R. Rapp:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.15/WW70

Topic: H.12. Aging and Development

Title: Amnestic Mild Cognitive Impairment And Alcohol Use Disorder Display Greater Functional Brain Network Similarities With Each Other Than With Healthy Controls

Authors: *G. WARNER, J. JOSEPH;
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Abstract: Alcohol Use Disorder (AUD) and amnestic mild cognitive impairment (aMCI) are both associated with altered functional connectivity in brain networks such as the episodic memory encoding network (EMN), default mode network (DMN), and frontoparietal network (FPN). AUD is also a risk factor for aMCI. Given this information it is surprising that so little has been done to directly compare network connectivity in these two groups. Such similarities could point to a mechanism through which AUD increases the risk of aMCI. To address this possibility, we conducted a study comparing resting-state fMRI networks of 22 AUD, 110 aMCI, and 84 healthy control (HC) to determine the similarities and differences of brain network connectivity based on independent component analyses (ICA) composition between these three groups. The hypothesis was that network composition in the AUD and aMCI group would be similar to each other while both being dissimilar to the HC group. Three ICA's were conducted, one for each of the three subject groups. The identified components were then manually labeled as part of the EMN, DMN, or FPN. Three series of cross correlations between the resulting

components, one for each group pairing, were conducted followed by chi-square analyses to compare the frequency of shared components. As predicted, the aMCI DMN components showed greater overlap with the AUD DMN components than with the HC DMN components (X^2=5.34, p=0.021). Similarly, the AUD DMN components showed greater overlap with the aMCI DMN components than with the HC DMN components (X^2=4.37, p=0.037). The aMCI EMN components showed a trend towards greater overlap with AUD EMN components than HC EMN components (X^2=3.82, p=0.051). In a second analysis, we performed a single ICA on the three groups (which were now matched by fMRI data acquisition TR) followed by a dual regression analysis which revealed that the FPN of both the AUD and aMCI groups included a region of the left hippocampus which was not included in the HCs. As the hippocampus is canonically associated with the EMN these findings suggest that perturbed resting-state networks may recruit regions from other networks in order to maintain functionality. These findings taken together indicate that aMCI and AUD show greater similarity of EMN, DMN, and FPN networks as compared to HCs.

Disclosures: G. Warner: None. **J. Joseph:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.16/WW71

Topic: H.12. Aging and Development

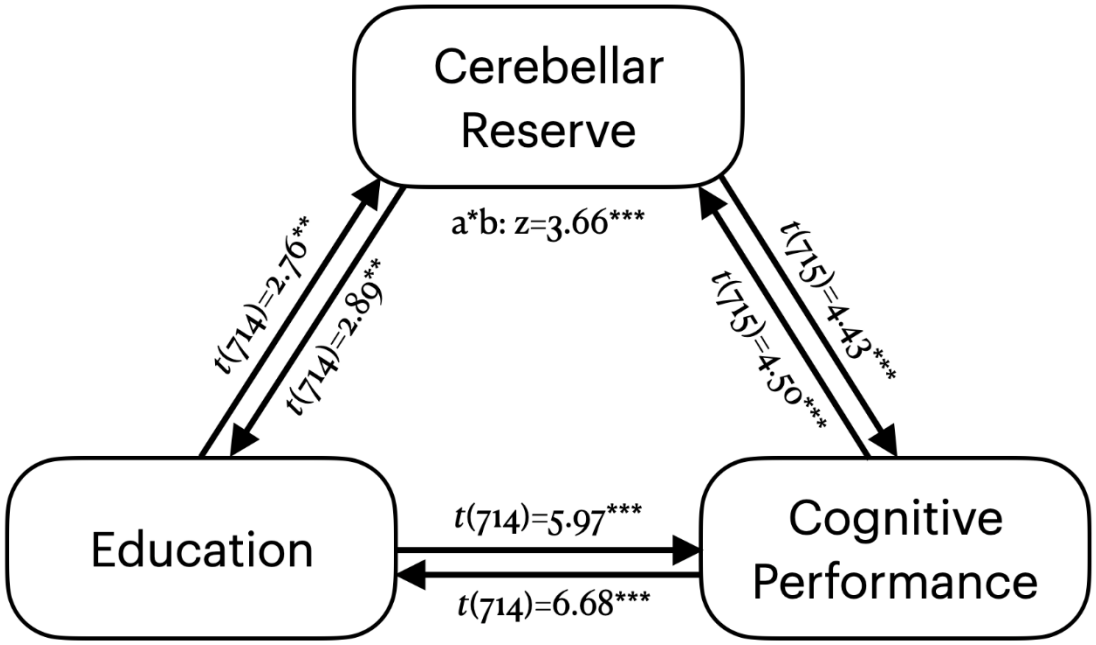
Support: National Science Foundation Graduate Research Fellowship
Ford Foundation National Academies of Sciences, Engineering and Medicine Predoctoral Fellowship
NIH R01 NS045193
NIH R01 MH115750

Title: Cerebellar reserve mediates associations of educational attainment and cognitive performance in healthy older adults

Authors: *F. D'OLEIRE UQUILLAS[1], J. MERRIMAN[1], E. SEFIK[1], J. SEIDLITZ[2], V. ZHANG[1], M. KISLIN[1], J. D. COHEN[1], F. KRIENEN[1], J. SEPULCRE[3], S. S.-H. WANG[1], J. GOMEZ[1];
[1]Princeton Univ., Princeton, NJ; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]MGH, Harvard Univ., Charlestown, MA

Abstract: Greater educational attainment in older adults has been associated with greater cortical volume and lower risk for dementia and cognitive decline, with mixed findings. Associations of educational achievement (7-21, years) with brain volumes were examined in healthy older adults (age: 36-100 years) from the Human Connectome Project (N720, 56% F). All statistical models included sex at birth, estimated intracranial volume (eTIV), and age as covariates.

In separate robust regression models, greater number of years of education were related with greater Montreal Cognitive Assessment (MOCA) total scores (Cohen's f=0.23, p<0.0001), and greater cerebellar volume (Cohen's f=0.10, p=0.006), but not cerebral cortex volume (p=0.865). Greater cerebellar volume was also related to greater MOCA scores (Cohen's f=0.17, p<0.0001). Mediation models revealed that education exerted its effect on MOCA cognition scores through cerebellar volume (a*b: z=3.6, bca 95% CI=0.02,0.06, p<0.0001). Cerebellar volume was not a moderator of education (education x cerebellar volume effect: p=0.672), nor MOCA scores (MOCA x cerebellar volume effect: p=0.669).
LASSO regression on individual cerebellar lobules, controlling for sex and eTIV, found that years of education were most related to left lobules I-III, VIIB, VIIIB and X, as well as bilateral lobules VI and VIIIA, and right Crus II (Bonferroni-corrected, p<0.05). MOCA cognitive scores were most related to higher-order cerebellar regions: left Crus I, Crus II, and Lobule VI (Bonferroni-corrected, p<0.05).
This is the first study to show a relationship between educational attainment and the cerebellum, and that educational attainment is a predictor of cognitive performance in older adults by way of cerebellar volume.



Disclosures: F. d'Oleire Uquillas: None. **J. Merriman:** None. **E. Sefik:** None. **J. Seidlitz:** None. **V. Zhang:** None. **M. Kislin:** None. **J.D. Cohen:** None. **F. Krienen:** None. **J. Sepulcre:** None. **S.S. Wang:** None. **J. Gomez:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.17/WW72

Topic: H.12. Aging and Development

Title: Proof of concept(POC) validation test for personalized near-infrared LED therapy based on QEEG

Authors: *U. PARK[1], J. KO[1], B. CHOI[1], H. KIM[1], H. LEE[1], H. GWAK[1], H. NA[1], J. KIM[2], D. KIM[1], S. KANG[1,3];
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Abstract: Near-infrared LED therapy is being actively researched as a form of electroceuticals for enhancing brain neurology through photobiomodulation. In particular, 850nm near-infrared light has been found to stimulate the mitochondria of brain cells within the cerebral cortex, increasing ATP production and promoting activation, as well as facilitating increased blood flow and neurological activity. This study aimed to investigate the clinical impact of LED therapy on individuals with degenerative brain diseases at a community level and examine the positive effects of LED therapy on QEEG patterns. A total of 53 participants, including 12 males and 41 females, with an average age of 73.3, were enrolled in the study. Participants with a Clinical Dementia Rating (CDR) score of 0.5 or higher received expert counseling to confirm the presence of degenerative brain diseases. The intervention lasted for 12 weeks, during which baseline and post-intervention measurements of QEEG, CDR scores, quality of life scales, and individual interviews were conducted to assess the efficacy of the proof of concept. The iSyncWave, a 10-20 system EEG measurement device developed by iMediSync, was used to collect data. This device incorporated near-infrared LED light-emitting diodes into each electrode, enabling personalized therapy protocols based on the participant's QEEG patterns. LED therapy was administered three times per week, with the LED region and frequency adjusted based on individual patterns identified from the baseline brainwave measurements. The results showed significant improvements in cognitive function, as measured by CDR (Before: 0.542, After: 0.062, p-value < 0.001). The relative delta power, a key pattern associated with cognitive decline and degenerative brain diseases in the prefrontal cortex, also decreased (Before: 0.222, After: 0.189, p-value < 0.05). The small-worldness, a brain network index related to information exchange efficiency, increased significantly overall (Alpha; Before: 0.043, After: 0.05, p-value < 0.05), and the overall scores of the quality of life scale showed a significant improvement. Specifically, there were significant improvements in sleep (Before: 3.0, After: 4.0, p-value < 0.001) and energy (Before: 3.0, After: 3.5, p-value < 0.0001). These results demonstrate the effectiveness of personalized LED therapy in enhancing cognitive function, as evidenced by both cognitive function assessments and quantitative analysis of physiological signals. Non-invasive and free from side effects, personalized LED therapy protocols hold great promise in the prevention and treatment of cognitive impairment patients.

Disclosures: **U. Park:** None. **J. Ko:** None. **B. Choi:** None. **H. Kim:** None. **H. Lee:** None. **H. Gwak:** None. **H. Na:** None. **J. Kim:** None. **D. Kim:** None. **S. Kang:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

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Program #/Poster #: PSTR307.18/WW73

Topic: H.12. Aging and Development

Support: CIHR Grants PJT162292; PJT162274
Alzheimer Society Research Program
James S. McDonnell Foundation Scholar Award
Ontario Graduate Scholarship

Title: Understanding the role of anterolateral entorhinal cortex in configural processing across the lifespan

Authors: *N. LADYKA-WOJCIK[1], S. D. ALLEN[2], J. C. LIANG[1], J. D. RYAN[1,3], R. K. OLSEN[1,3], M. D. BARENSE[1,3];
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Abstract: The entorhinal cortex (ERC) is one of the earliest regions impacted in age-related pathologies like Alzheimer's Disease (AD), even before clinical diagnosis. Mounting evidence in humans and non-human animals has identified two subdivisions of ERC: an anterolateral (alERC) and a posteromedial (pmERC) subregion. Recent work also suggests that alERC volume in older adults, in contrast to pmERC volume, predicts intra-item configural processing (i.e., the ability to process arrangements between an object's features, reflected in eye movements). However, a functional role for the alERC in configural processing remains unclear, particularly in predicting cognitive decline associated with preclinical AD. In the current study, we used functional magnetic resonance imaging (fMRI) with simultaneous eye-tracking to investigate the relationship between functional patterns in alERC and intra-item configural processing across the lifespan. Our study included a large sample of younger (n = 48) and older (n = 51) adults, the latter demonstrating a range of cognitive performance from normal aging to at-risk for AD-related cognitive decline based on the Montreal Cognitive Assessment. Within each block of the experiment, participants were shown five repetitions of three computer-generated conjunctive objects comprised of distinct upper and lower halves. On the sixth and seventh repetitions of each block, we assessed the effect of novelty for whole objects by presenting participants with three possible configurations: (1) an old object configuration from prior repetitions in the block; (2) a reconfigured object in which the two halves had been presented as parts of different objects in the block; and (3) a novel object in which both halves were new. Finally, we used manually segmented subject-specific masks of the alERC and surrounding medial temporal lobe regions to constrain our functional analyses. Our results revealed an age-related pattern of activation along the ventral visual stream from early visual areas towards the alERC for novel and recombined objects compared to old objects. Overall, our results provide first evidence for the relationship

between functional activity in the alERC and configural novelty, mediated by age and cognitive performance.

Disclosures: N. Ladyka-Wojcik: None. **S.D. Allen:** None. **J.C. Liang:** None. **J.D. Ryan:** None. **R.K. Olsen:** None. **M.D. Barense:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.19/WW74

Topic: H.12. Aging and Development

Support: National Science Foundation Graduate Research Fellowship (FdU)
Ford Foundation National Academies of Sciences, Engineering, and Medicine Predoctoral Fellowship (FdU)

Title: A Role for Cerebellum in Cognitive Aging and Brain Reserve

Authors: *J. MERRIMAN[1], F. D'OLEIRE UQUILLAS[1], E. SEFIK[1], J. SEIDLITZ[2], J. D. COHEN[1], J. SEPULCRE[3], J. GOMEZ[1];
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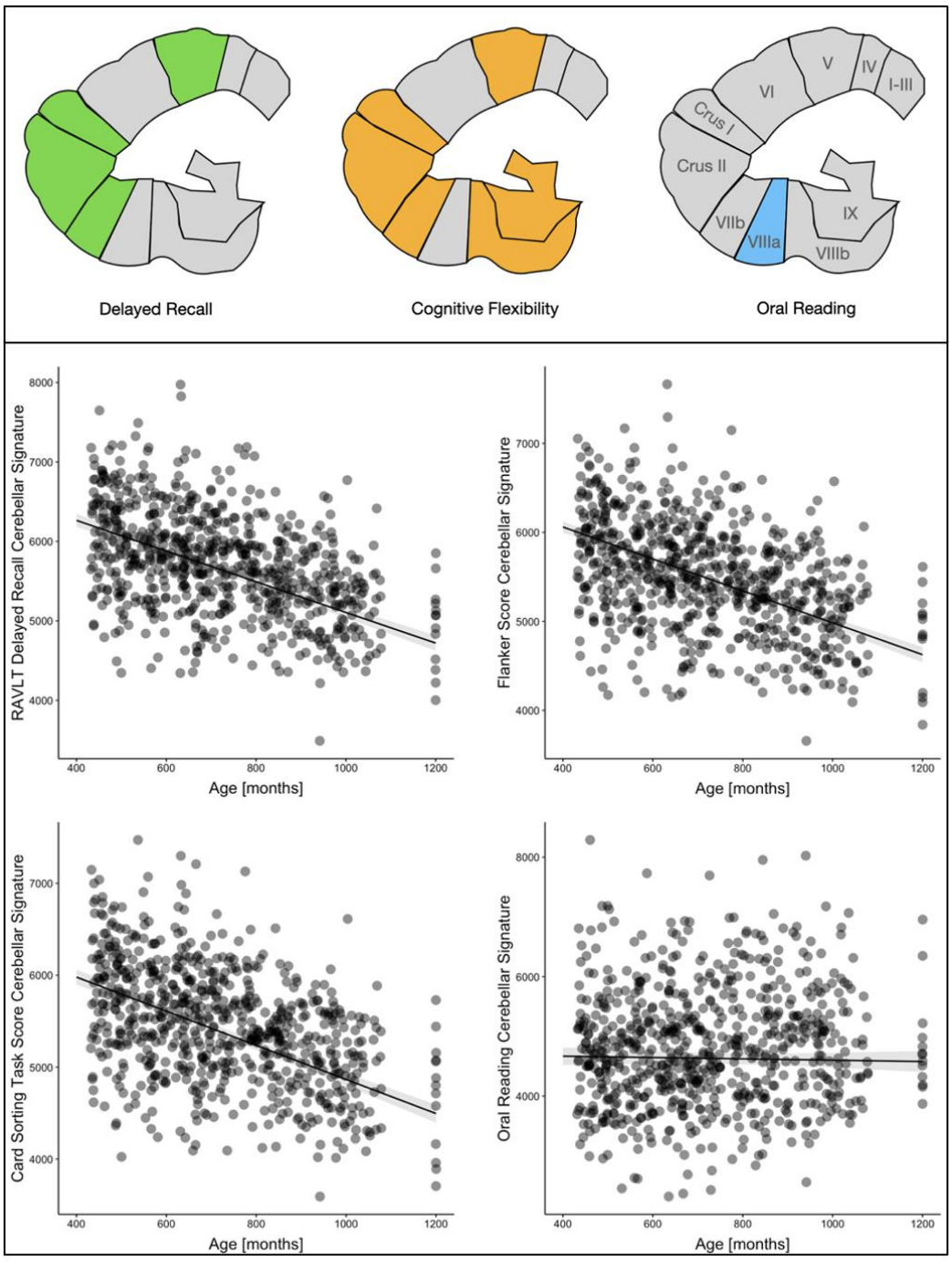
Abstract: Cerebellar reserve refers to the capacity of the cerebellum to compensate for the cognitive effects of brain injury, including from biologically driven age-related processes. Here we sought to discover novel subtypes of cerebellar reserve for different cognitive domains in healthy older adults from the Human Connectome Project (n725, 56% F, age range: 36-100, years; mean=60.28).
Using LASSO regression, we first mapped associations between cerebellar regional volumes and specific cognitive domains: cognitive flexibility (Dimensional Change Card Sort, DCCS; and Flanker Inhibitory Control and Attention Task), reading decoding (Oral Reading Recognition Test, ORRT), and delayed memory recall (Rey Auditory Verbal Learning Test, RAVLT; and Face-Name Associative Memory Exam, FNAME Recall). We found that higher Delayed Memory Recall scores commonly related to greater volumes in left Crus I, II, and Lobule V, VIIb. Cognitive Flexibility commonly recruited a more distributed pattern of regions in addition to Crus I and II, while Right Lobule VIIIa only related to Oral Reading. We next averaged the relevant cerebellar regional volumes for each cognitive task to create cerebellar reserve signatures, which represented the relationship between cerebellar volume for that lobule and the cognitive task. We characterized the volumetric trajectories across the observed age range and found linear effects of age (RAVLT: β=-1.93, se=0.1, Cohen's f=0.72, p<0.0001; FNAME Recall: β=-2.29, se=0.11, Cohen's f=0.73, p<0.0001; DCCS: β=-1.86, se=0.1, Cohen's f=0.72, p<0.0001; Flanker: β=-1.77, se=0.1, Cohen's f=0.70, p<0.0001). We also found that among older adults, greater levels of cerebellar signature volume conferred greater cognitive scores (DCCS:

p=0.012).
Here we find overall evidence for cerebellar cognitive reserve and unveil age-related patterns of cerebellar volumetric associations with cognitive performance. Further work is underway to investigate how socioeconomic status and ethnicity may influence associations between cerebellar volume and cognitive performance.



Disclosures: **J. Merriman:** None. **F. d'Oleire Uquillas:** None. **E. Sefik:** None. **J. Seidlitz:** None. **J.D. Cohen:** None. **J. Sepulcre:** None. **J. Gomez:** None.

Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.20/WW75

Topic:

Support: NIH (5K07AG06026602)
VA Merit Review (BX000758)
Indian Trail Foundation

Title: Nicotinamide riboside increases cognitive function and decreases microglial activation in aged mice.

Authors: *R. THIYAGARAJAN, R. BERMAN, Y. REDAE, O. TREANOR, A. DAVIS, K. SELDEEN, B. TROEN;
Univ. of Kansas Med. Ctr., Kansas City, KS

Abstract: Abstract: As many as 1 in 6 people ages 60 or older exhibit cognitive impairment, representing major challenges for healthcare infrastructure as this demographic is projected to reach more than 75 million by 2030. Microglia undergo dramatic changes during aging and exhibit dysfunction that coincides with cognitive decline. Nicotinamide adenine dinucleotide (NAD+) is an essential co-enzyme for mitochondrial function, decreases with aging, and contributes to age-related declines in cellular metabolism and function. The NAD precursor, nicotinamide riboside (NR), restores cellular NAD+ levels in aged mice. But the impact of NR supplementation on microglia gene expression and cognitive function is yet to be elucidated. We provided 21-month-old male C57BL/6JNIA mice with chow containing placebo (PLB, $n = 10$) or NR at a dose of 400 mg/kg mouse weight (NR, $n = 10$). After 12 weeks, NR supplementation significantly enhanced the number of spontaneous alternations in Y-maze ($p < 0.05$), a measure of memory and exploratory activity, and prevented the age-related decline in nest-building ability, a measure corresponding to the housework component of the instrumental activities of daily living. NR also increased total NAD+ in muscle but not in the brain. Messenger RNA and microRNA sequencing were performed using NovaSeq 6000 System on magnetically sorted microglia from the whole brains of PLB, NR, and young mice. Gene expression analysis revealed greater activation, inflammation, and mitochondrial dysfunction in microglia from aged mice compared to young mice. In contrast, microglia from the NR-supplemented aged mice showed a lower activation status and a gene expression profile more similar to young mice. Therefore, NR supplementation enhances memory and an instrumental activity of daily living and concomitantly improves the microglia gene expression profile reflecting less activation and inflammation and better mitochondrial function. These findings support the translation of this work into clinical settings to ascertain the benefits of NR supplementation for maintaining and enhancing functional and cognitive activity during aging.

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Poster

PSTR307. Cognitive Natural Aging: Behavior and Cognitive Disorders

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR307.21/WW76

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Activation of the apelin receptor, implicated in a key aging pathway by analysis of longitudinal human data, ameliorates multiple mechanisms that drive neuroinflammation and neurodegeneration

Authors: *A. J. B. LUNDQUIST, Z. O'BROWN, N. SHAH, R. HUGHES, P. LEONG, E. MORGEN, K. FORTNEY;
BioAge Labs, Inc., Richmond, CA

Abstract: We developed a discovery platform based on analysis of multi-omic data from proprietary longitudinal human aging cohorts to identify novel targets for diseases of aging. Our analyses using the platform revealed a novel connection between higher circulating levels of apelin, and beneficial outcomes including delayed mortality and preservation of muscle and cognitive function. Apelin is a peptide hormone widely expressed throughout the body that signals through its Gi/o protein-coupled receptor APJ to exert beneficial effects on cellular function. Within the central nervous system, APJ is primarily expressed in astrocytes, which play important roles in age-related neuroinflammation and neurodegeneration. We observed that apelin pathway activity decreases with age. In multiple preclinical models of neurodegeneration, direct brain administration of apelin peptide has disease-modifying effects via modulation of apoptosis, inflammation, and autophagy. Based on the connection between apelin and cognitive aging, along with the established relationship between apelin, inflammation, and neurodegeneration, we hypothesized that apelin pathway activation could decrease inflammatory signaling in astrocytes. Using BGE-105, a highly selective, potent, orally available small-molecule agonist of the apelin receptor APJ, we demonstrated that astrocytic apelinergic signaling mediates potent anti-inflammatory and neuroprotective effects. We generated a model of the neuroinflammation associated with aging and neurodegeneration by stimulating primary mouse astrocytes using IL-1α/TNF-α/C1q. In these stimulated astrocytes, BGE-105 robustly inhibited proinflammatory cytokine release via downregulation of NF-κB. Activation of the astrocyte apelin pathway also increased glutamate uptake by increasing GLT1 expression. Because neuroinflammation causes breakdown of the blood-brain barrier (BBB), we examined the effect of BGE-105 on aged (26-month-old) mice. Daily oral administration of BGE-105 for 7 days suppressed circulating levels of age-related proinflammatory cytokines, increased levels of BDNF in the hippocampus, and reversed age-induced BBB dysfunction, suggesting that BGE-105 restores the BBB through its anti-inflammatory effects in the periphery. Taken together, our results suggest that apelin receptor agonism with an orally available small molecule represents a

novel approach for treating chronic age-related neuroinflammation and neurodegeneration, and for mitigating the effects of inflammation on the BBB.

Disclosures: A.J.B. Lundquist: A. Employment/Salary (full or part-time):; BioAge Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAge Labs. **Z. O'Brown:** A. Employment/Salary (full or part-time):; BioAge Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAge Labs. **N. Shah:** A. Employment/Salary (full or part-time):; BioAge Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAge Labs. **R. Hughes:** A. Employment/Salary (full or part-time):; BioAge Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAge Labs. **P. Leong:** A. Employment/Salary (full or part-time):; BioAge Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAge Labs. **E. Morgen:** A. Employment/Salary (full or part-time):; BioAge Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAge Labs. **K. Fortney:** A. Employment/Salary (full or part-time):; BioAge Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAge Labs.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.01/WW77

Topic: I.03. Anatomical Methods

Title: Understanding vision with Drosophila connectomics

Authors: *F. LOESCHE, A. NERN, S.-Y. TAKEMURA, J. HOELLER, N. C. KLAPOETKE, E. GRUNTMAN, K. D. LONGDEN, S. KOSKELA, E. M. ROGERS, P. SEENIVASAN, A. ZHAO, M. DREHER, G. M. RUBIN, M. B. REISER;
Janelia Res. Campus, Ashburn, VA

Abstract: The fly visual system provides a unique opportunity to study neural networks solving known (or knowable) computational tasks. Decades of anatomical studies have carefully cataloged many of the cell types in the visual system, and in parallel, decades of behavioral and physiological experiments have examined the visual capabilities of flies. The wealth of interesting, high-performance visual behaviors coupled with genetic tools for targeted access to nearly any neuron type in the brain, have made *Drosophila* an outstanding system to study the neural circuit implementation of many computations. Janelia's FlyEM team has successfully imaged the complete nervous system of an adult, male fruit fly using Focused Ion Beam milling and Scanning Electron Microscopy (FIB-SEM). Subsequently, the entire volume was

reassembled and Google Research's connectomics group carried out automatic segmentation of the volume into neuron fragments, which were then proofread by connectome annotators at Janelia. The right optic lobe is the first brain region that was proofread. We then cataloged all neurons in the optic lobe, including the complete medulla (and accessory medulla), lobula, lobula plate, and approximately half of the lamina. Using first morphology analysis and then iterations of connectivity analysis, we identified and named all cell types of the optic lobe—over 51,000 neurons in ~700 cell types. Such that we now have access to a complete, curated, connectome of an entire fly optic lobe. For the first time, this data set allows a quantitative analysis of the flow of information across neuropils, such as the tracing of retinotopy from the retina and lamina through to the medulla, lobula, and lobula plate. Specifically, we examine the highly stereotyped columnar structure with its similarities and differences across the whole eye. Access to this wealth of information is critical for future analysis, particularly in the context of making strong inferences for predicting neuron function and for reevaluating prior experimental results. Here, we will detail a method to register single neurons to a specific address based on their morphology, location, and connectivity, and will demonstrate how to use this address space to enable new analyses.

Disclosures: **F. Loesche:** None. **A. Nern:** None. **S. Takemura:** None. **J. Hoeller:** None. **N.C. Klapoetke:** None. **E. Gruntman:** None. **K.D. Longden:** None. **S. Koskela:** None. **E.M. Rogers:** None. **P. Seenivasan:** None. **A. Zhao:** None. **M. Dreher:** None. **G.M. Rubin:** None. **M.B. Reiser:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

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Program #/Poster #: PSTR308.02/WW78

Topic: I.03. Anatomical Methods

Support: NIH R01-EB026439
NIH U24-NS109103
NIH P41-EB018783
NIH U01-NS108916
NIH R01-NS101013
NIH R01-CA203861
NIH R01-NS104500
NIH U01-NS128612

Title: Investigating Human Cingulate Cortex Connectivity Through Intracranial Single Pulse Stimulation

Authors: *P. DEMAREST[1,2,4,3], M. ADAMEK[1,2], J. R. SWIFT[1,2,3], T. XIE[1,2,3], J. T. WILLIE[1,2,3], P. BRUNNER[1,2,3,4], E. C. LEUTHARDT[1,2,3,4];

[2]Div. of Neurotechnology, [3]Dept. of Neurosurg., [1]Washington Univ. Sch. of Med., Saint Louis, MO; [4]McKelvey Sch. of Engin., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: The cingulate cortex is widely recognized as a key locus that orchestrates various cognitive, perceptual, and behavioral processes. In humans, this region is an attractive target for neuromodulation to treat various disorders such as chronic pain or depression. This is specifically due to its intricate cortical connectivity, functionally and anatomically distinct sub-regions, and involvement in processes such as emotional affect and sensory integration. We recently conducted a six-week brain-computer interface intervention study with patients suffering from chronic pain and identified a significant relationship between pain symptom relief and patient-mediated increases in frontal theta power (Spearman's Rho 0.33, $p < 0.01$). Previous evidence suggests that this electrophysiological activity pattern indicates activity from the anterior cingulate cortex. While the clinical outcomes of this study are promising, they do not provide robust insight into the neurophysiological mechanisms driving patient symptom relief. The present study aims to provide direct, spatially specific, intracranial evidence of cingulate connectivity in humans through invasive single pulse stimulation to thus bolster our current understanding of the underlying physiology that may contribute to pain relief in humans. Five patients with intractable epilepsy invasively monitored using stereotactic electroencephalography underwent bipolar single-pulse stimulation of either the anterior cingulate cortex, midcingulate cortex, or posterior cingulate cortex at 3mA or 6mA. Cingulate sub-regional connectivity was then investigated by analyzing cortico-cortical evoked potentials at recording electrodes within the hippocampus, amygdala, frontal cortex, and somatosensory cortex. Evoked local activity within these regions was then represented by changes in high gamma. Finally, evoked potentials detected by electrodes on the patient's scalp provide valuable evidence linking evoked activity within the cingulate cortex, and electrophysiology recorded using surface EEG. The results of this study provide robust electrophysiological representations of cingulate connectivity and provide valuable insights into the nuanced inter-regional dynamics of this area.

Disclosures: **P. Demarest:** None. **M. Adamek:** None. **J.R. Swift:** None. **T. Xie:** None. **J.T. Willie:** None. **P. Brunner:** None. **E.C. Leuthardt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurolutions, Sora Neuroscience, Inner Cosmos.

Poster

PSTR308. Connectomics: Central Nervous System

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Program #/Poster #: PSTR308.03/WW79

Topic: I.03. Anatomical Methods

Support: Boston University Center for Systems Neuroscience Distinguished Fellowship
1F32MH129149-01A1

1RF1MH126882-01A1
S10OD024993

Title: A scalable approach for mapping connectivity of transcriptomically defined neuron types

Authors: ***M. MOYA**[1,2], W. J. CUNNINGHAM[1,3], A. ZAMBON[1], T. WANG[6], M. N. ECONOMO[1,2,4,5];
[1]Biomed. Engin., [2]Ctr. for Systems Neurosci., [3]Grad. Program for Neurosci., [4]Ctr. for Neurophotonics, [5]Photonics Ctr., Boston Univ., Boston, MA; [6]Janelia Res. Campus, Ashburn, VA

Abstract: Large-scale transcriptomic atlasing projects have uncovered the vast diversity of cell types that compose each brain region. But defining the connectivity of the thousands of cell types in the brain remains challenging due to a lack of scalable methods. By combining high-sensitivity fluorescence voltage imaging and optogenetic photostimulation, we have developed an approach to map synaptic connectivity between brain regions with up to 100x greater throughput than existing techniques. Importantly, the all-optical basis of this method allows us to readily integrate synaptic connectivity measurements with highly multiplexed fluorescence *in situ* hybridization. In this way, we can molecularly identify large populations of neurons as well as describe their connectivity. Here, we demonstrate a proof-of-concept of this synaptic mapping approach (SYNMAP) in the motor cortex, providing a framework for performing high-throughput connectivity mapping across any brain region of interest. Population-level data acquired with SYNMAP have the potential to rapidly advance our understanding of how the diverse cell types of the brain are wired to form the functional circuits that underlie all cognition, learning, and behavior.

Disclosures: M. Moya: None. **W.J. Cunningham:** None. **A. Zambon:** None. **T. Wang:** None. **M.N. Economo:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.04/WW80

Topic: I.03. Anatomical Methods

Support: NHMRC grants (APP1086083, APP1086643)
ARC Center of Excellence for Integrative Brain Function (CE140100007)
NIH P41 EB015897 and NIH 1S10OD010683

Title: Mri/dti atlas of the human brainstem in transverse and sagittal planes

Authors: G. PAXINOS[1], T. FURLONG[2], K. W. ASHWELL[2], ***K. SMITH**[1], E. CALABRESE[3], G. A. JOHNSON[4];

[1]Neurosci. Res. Australia, [2]Univ. of New South Wales, Randwick, Australia; [4]Radiology, [3]Duke Univ., Durham, NC

Abstract: Conventional imaging atlases of the human brain have been constructed using low spatial resolution MRI, rendering neuroanatomical delineations unsatisfactory compared to histological maps. **W**e aimed to construct an MRI atlas of the human brainstem using considerably higher resolution/contrast than currently available, with neuroanatomical delineations guided by those identified in our histological atlas of the human brainstem[1]. **P**ostmortem MR imaging was performed on a human brainstem of a 65-year-old male with no history of neurologic or psychiatric conditions in a 7T machine. Anatomic images were acquired using a 3D gradient echo pulse sequence, and diffusion data using a simple diffusion-weighted spin echo pulse sequence. Brain structures were manually traced in the transverse and sagittal planes. Delineations were informed by histology where available. **T**he 50μm GRE and 200μm DTI resolution images obtained to construct this atlas are 8000x and 1000x higher than the average clinical structural MRI and DTI, respectively. The high resolution of this data set enabled us to successfully delineate 363 structures (more than 80% of that identified in our histological atlas[1]) and produced 86 detailed diagrams across the transverse and sagittal planes using GRE, FAC, and DWI images. **W**e have constructed an MRI/DTI atlas of the human brainstem using data of unprecedented quality, that is also the first to present detailed diagrams in the sagittal plane, giving a unique perspective on brainstem organisation.

Disclosures: G. Paxinos: None. **T. Furlong:** None. **K.W. Ashwell:** None. **K. Smith:** None. **E. Calabrese:** None. **G.A. Johnson:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.05/WW81

Topic: I.03. Anatomical Methods

Title: Pattern of cortical white matter terminations across thalamus is conserved across primates.

Authors: *A. M. HOWELL[1], S. WARRINGTON[4], C. FONTENEAU[5], Y. CHO[2], S. N. SOTIROPOULOS[4], J. D. MURRAY[3], A. ANTICEVIC[1];
[1]Psychiatry, [3]Dept. of Psychiatry, [2]Yale Univ., New Haven, CT; [4]Univ. of Nottingham, Nottingham, United Kingdom; [5]Dept. of Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: Corticothalamic anatomical connections vary between sensory and association systems along the cortical hierarchy (Harris et al., 2019). Previous work using diffusion weighted imaging (DWI) in humans and macaque monkeys has demonstrated that some cortical areas may project to multiple thalamic nuclei (Zhang et al., 2010; Phillips et al., 2019). However, the spread of thalamic connectivity patterns has not been systematically examined for every cortical area and so it remains unclear if such spread differs between sensory and association corticothalamic

circuits. In this study, we tested the hypothesis that the spread of thalamic connectivity patterns varied between sensory and association cortical areas in primates. Using probabilistic tractography data from healthy adults from the Human Connectome Project (n=828) and post-mortem macaques (n=6), the spread of each cortical area's tractography pattern across the thalamus was quantified using Principal Components Analysis (PCA) on Euclidean distance (ED) values across 100 thresholds for 360 cortical parcels (EDpc1) for each subject. Here, higher EDpc1 values correspond to more diffuse, or spread out, thalamic connectivity. The T1w/T2w ratio is a proxy measure of myelin and it is lower in association cortical areas (Burt et al., 2018). We correlated each subject's EDpc1 values and T1w/T2w ratio values using spearman correlation (rs). EDpc1 loadings dissociated cortical areas with focal and diffuse thalamic connectivity in humans and macaques. Notably, humans and macaques had similarly focal motor area 1 (M1) thalamic terminations, but human dorsolateral prefrontal cortex (DLPFC) thalamic terminations were more diffuse than that of macaques. EDpc1 loadings were significantly positively correlated with T1w/T2w values at the group-level in both humans ($p = 0.025$) and macaques ($p = 0.014$), such that sensory cortical areas had more focal thalamic terminations relative to association cortical areas. We characterized the variability of this relationship across subjects and, on average, there was a moderate correspondence between EDpc1 loadings and T1w/T2w values in both human (Mdn = 0.35) and macaque (Mdn = 0.34) subjects. Overall, we found that sensory cortical areas have more focal terminations across thalamus relative to association cortical areas in both humans and macaques. Additionally, we observed interspecies differences in the spread of some cortical areas (e.g. DLPFC). Future studies will further investigate these differences in homologous primate brain areas.

Disclosures: **A.M. Howell:** None. **S. Warrington:** None. **C. Fonteneau:** None. **Y. Cho:** None. **S.N. Sotiropoulos:** None. **J.D. Murray:** None. **A. Anticevic:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

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Program #/Poster #: PSTR308.06/WW82

Topic: I.03. Anatomical Methods

Support: Supported by the Francis Crick Institute which receives its core funding from Cancer Research UK (CC2108), the UK Medical Research Council (CC2108), and the Wellcome Trust (CC2108)

Title: High throughput molecular connectomics with barcoded rabies viruses

Authors: *A. BECALICK, A. BLOT, M. STROM, P. ZNAMENSKIY;
The Francis Crick Inst., London, United Kingdom

Abstract: Conventional approaches for determining the connectivity of individual neurons are extremely labor-intensive and limited to reconstructing connections between nearby neurons -

within 100s of microns. Recently, methods relying on DNA sequencing of unique oligonucleotide “barcodes” have been proposed for high-throughput reconstruction of neuronal connectivity. To date, they have been successfully applied to systematically characterize long-range projection patterns of thousands of neurons in parallel. However, existing approaches lack the resolution to identify individual synaptic connections. Taking advantage of the ability of rabies virus to spread between connected neurons, we developed a new method that has the potential to map thousands of synaptic connections within a single experiment. Infecting a population of starter cells with a library of rabies viruses expressing random barcode sequences enables these cells to transmit their barcodes to their direct presynaptic partners. These barcodes can then be matched to their respective starter cells to reconstruct synaptic connections. Towards this goal, we have generated libraries of barcoded rabies viruses with sufficient diversity to uniquely label >1000 starter cells within a single experiment. We used the CVS-N2c strain of rabies virus, which exhibits reduced cytotoxicity, in order to maintain viability of infected neurons. To preserve information about the spatial location of barcoded cells and avoid cell loss resulting from tissue dissociation, we used in situ sequencing to read out viral barcodes alongside endogenous transcripts of cell type marker genes from intact sections of mouse brain. This enabled us to classify the cell types of barcoded neurons, making it possible to relate their connectivity and molecular identity. As a proof-of-concept, we are currently applying this method to characterize cell-type specific connectivity rules in the mouse primary visual cortex. Our approach is highly scalable, does not depend on the availability of cell-type specific transgenic lines, and can be readily translated across brain areas, enabling the systematic characterization of connectivity between cell types in the mammalian brain.

Disclosures: **A. Becalick:** None. **A. Blot:** None. **M. Strom:** None. **P. Znamenskiy:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.07/WW83

Topic: I.03. Anatomical Methods

Title: Automated neuropil segmentation of fluorescent images for Drosophila brains

Authors: *K. HSU[1], C.-T. SHIH[2], N.-Y. CHEN[3], C.-C. LO[1];
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Abstract: The connectomic study is one of the most important research domains in today’s neuroscience. Connectomic analysis usually involves warping and registering individual brain images into a standard brain template. However, warping and registration often produce large spatial errors (1~3μm) and hence severely reduce the accuracy of the connectomic analysis. To address this issue, we have developed a method for automatically segmenting neuropils in individual fluorescent images of *Drosophila* brains obtained from the *FlyCircuit* database. This

technique enables future connectomics research to be conducted without the need for warping and registration to a standard brain template.Our method includes two stages. In the first stage, we use the YOLO model to locate neuropils and rapidly extract small-scale 3D images, which serve as input for the subsequent model in the second phase. In the second stage, we use the 3D-UNet model for neuropil segmentation. Our initial findings reveal a 99.4% accuracy rate in brain region localization during the first stage. In the second stage, we only use 3D images from 15 brains for training and achieve satisfactory accuracy in segmenting the antennal lobe (AL) and mushroom body (MB). For the test set performance, the F1 score is 0.93, and the 3D-IoU reaches 0.89. This outcome is comparable to the human labeling, which yields 3D-IoU between 0.85 and 0.89 3D-IoU for the same neuropils by two professional labelers. We also demonstrate that our method can be applied to other neuropils in *Drosophila*.Our method attains the proficiency of human labelers while taking only a mere 7 seconds to segment an AL or MB for one brain. Hence, the method constitutes a critical component in the high throughput connectome construction for optical imaging of the *Drosophila* brain.

Disclosures: **K. Hsu:** None. **C. Shih:** None. **N. Chen:** None. **C. Lo:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.08/XX1

Topic: I.03. Anatomical Methods

Support: R01MH129439
R01MH118257
T32EB031512
R25DA057802

Title: Structural Connectivity of the Posteromedial Cortex

Authors: *F. AGUILAR ORTEGA[1], Z. LIU[2], D. BULLOCK[3], J. ZIMMERMANN[2], S. R. HEILBRONNER[4];
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Abstract: The Posteromedial Cortex (PMC) is part of the brain's Default Mode Network (DMN). It is central to an impressive array of cognitive and emotional functions, but its structural connectivity has been relatively under-explored. Here, we utilize both anatomical tract-tracing (in macaques) and diffusion MRI tractography (in macaques and humans). In doing so, we are able to compare the ground truth of tract-tracing with the less invasive tractography approach. The qualitative comparison between tract-tracing and tractography data shows a substantial agreement, but there are glaring issues, particularly with regard to PMC-striatal

pathways. For tractography data, we ask three main questions: 1) What proportion of PMC fibers use each segmented bundle? 2) Where do each of these sets of fibers end? 3) How similar are the monkey and human PMC tractography fiber pathways? In both species, quantitative analyses reveal that PMC fibers primarily travel in the cingulum bundle and corpus callosum, with additional involvement of other bundles such as the middle longitudinal fasciculus and the internal capsule. Our findings offered valuable insights into the structural connectivity of the PMC, and ultimately we hope to enhance our understanding of its role within the DMN.

Disclosures: F. Aguilar Ortega: None. **Z. Liu:** None. **D. Bullock:** None. **J. Zimmermann:** None. **S.R. Heilbronner:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.09/XX2

Topic: I.03. Anatomical Methods

Support: NWO Open Science Fund 203.001.058

Title: Hippocampal Connectomics Revisited: An Improved (Para)Hippocampal Connectome Database Bridging Diverse Anatomical Nomenclatures

Authors: *N. M. VAN STRIEN[1], J. J. GEISLER[1], J. M. J. MURRE[1], M. P. WITTER[2], N. L. M. CAPPAERT[1];
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Abstract: The wiring diagram of the brain, i.e. its connectome, contains fascinating insights into its function. However, creating a comprehensive network chart is challenging due to the abundance of anatomical nomenclatures that are in use. To address this, we previously constructed a connectome of the rat hippocampal formation, parahippocampal region and retrosplenial cortex (Van Strien, 2009). Here, we present an advanced version of this connectome, characterized by several key improvements. Brain connectivity is now stored in a MySQL database using the original nomenclature, while translations to standardized terminology are enabled by an integrated nomenclature dictionary. This dictionary was created by individually translating over 4,000 neuroanatomical terms that are used in over 18,000 curated connections, into standardized terms. The nomenclature dictionary allows for a more comprehensive understanding of brain connectivity by accurately consolidating multiple reports of a connection, even when they employ different nomenclatures. Moreover, our updated database can store brain connectivity data from all species, obtained through various visualization techniques, supplemented with relevant metadata. Types of connectivity that were previously impossible to catalogue, such as brain connectivity to the hemisphere contralateral to location of the cell body, are now also curated. Likewise, connections that were explicitly

reported as absent are stored as well. Finally, the curators now differentiate between connections that are explicitly reported and those that are suggested implicitly, and therefore inferred from the articles. Incorporating these changes required an extensive reworking of the entire connectome. The new dataset can be filtered on a variety of labels (e.g. gender, species, method, rating, hemisphere) to identify relevant experiments and connections. The temporal-lobe.com website offers new interactive tabulations to view and filter the connectome dataset, providing an invaluable resource for neuroscientists worldwide.

Disclosures: **N.M. van Strien:** None. **J.J. Geisler:** None. **J.M.J. Murre:** None. **M.P. Witter:** None. **N.L.M. Cappaert:** None.

Poster

PSTR308. Connectomics: Central Nervous System

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.10/XX3

Topic: I.03. Anatomical Methods

Support: National Key R&D Program of China (2020YFE0205900)
Shanghai Municipal Science and Technology Major Project (2018SHZDZX05)
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Strategic Priority Research Program of the Chinese Academy of Sciences (XDB32010105)
National Natural Science Foundation of China (31771180, 91732106)
Shanghai Science and Technology Committee (2019-78677)

Title: Brain-wide organization of single-neuron projectomes of the mouse hippomcapus

Authors: *S. QIU[1], Y. HU[1], Y. HUANG[1], T. GAO[1], Y. SUN[1], C. LI[1], H. YAO[1], H. GONG[2], Y. SUN[1], C. XU[1], *S. QIU[1], *S. QIU[1], *S. QIU[3];
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Abstract: Mapping hippocampal single-neuron projections is essential for understanding brain-wide circuit organization and diverse functions of the hippocampus. We reconstructed single-cell projectome of 10,100 mouse hippocampal neurons and identified 43 projectome subtypes, each with distinct collateral axon projection targets and preferential soma location along hippocampal longitudinal and transverse axes. Many projectome subtypes were enriched in selective hippocampal subdomains defined by spatial transcriptomic patterns. Although some neurons in

CA1 and subiculum complex exclusively projected to the hippocampal formation (HPF), most projected to both intra- and extra-HPF targets with varying targeting patterns and projection strengths. Furthermore, bi-hemispheric projecting hippocampal neurons generally projected to one pair of homologous targets with ipsilateral preference. Finally, the total arbor length of the axon correlated with that of dendrites of each neuron in CA3, CA1 and subiculum complex. These organization principles of single-neuron projectome provide a structural basis for understanding diverse but coordinated functions of hippocampal neurons.

Disclosures: **S. Qiu:** None. **Y. Hu:** None. **Y. Huang:** None. **T. Gao:** None. **Y. Sun:** None. **C. Li:** None. **H. Yao:** None. **H. Gong:** None. **Y. Sun:** None. **C. Xu:** None. **S. Qiu:** None. **S. Qiu:** None. **S. Qiu:** None.

Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.11/XX4

Topic: I.03. Anatomical Methods

Support: Ministry of Science and Technology of China 2021ZD0202500
Shanghai Municipal Science and Technology Major Project 2018SHZDZX05
Strategic Priority Research Program of the Chinese Academy of Sciences XDB32000000

Title: Single-neuron projectomes of mouse paraventricular hypothalamic nucleus oxytocin neurons

Authors: *H. LI[1,2,3,4], T. JIANG[5], S. AN[6], L. GOU[2], B. REN[2], X. SHI[2], X. WANG[2], J. YAN[2], J. YUAN[5,6], X. XU[2], Q. LUO[5,6], H. GONG[5,6], W.-J. BIAN[2,7], A. LI[5,6], X. YU[1,2,3,4];
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Abstract: Oxytocin (OXT) is an evolutionarily conserved nonapeptide, which plays important roles in autonomic control and behavioral modulation, in species ranging from invertebrates to humans. OXT neurons localize to a number of brain regions, with the paraventricular hypothalamic nucleus (PVH) containing the largest number and most extensively arborized OXT neurons, likely holding the key to their central physiological functions. To better understand the

complex functions of OXT neurons, several previous studies analyzed the mesoscale projectomes of OXT neurons, especially PVH OXT neurons, using bulk labeling. While clearly illustrating the complexity of OXT neuron projection patterns, mesoscale experiments do not allow visualization of the diversity of individual OXT neuron projectomes, nor do they address whether the projectome of subtypes of OXT neurons have distinct patterns, possibly aligned with function. High resolution single-neuron projectomes, in addition to addressing the above questions, also allow analysis of co-projection relationships between brain regions, which is critical to understanding how projection patterns of individual neurons correlate with their functions.In order to label single OXT neurons brightly, sparsely and specifically, we designed and generated a Cre-dependent AAV construct which expressed cytoplasmic and membrane-bound fluorescent proteins in tandem. We used fluorescence micro-optical sectioning tomography (fMOST) technology to image the whole-brain projectome of single OXT neurons at submicron resolution, and Fast Neurite Tracer (FNT) software to reconstruct axons and dendrites of PVH OXT neurons. From 264 sparsely and brightly labeled PVH OXT neurons with complete 3D reconstructed axonal morphologies, by hierarchical clustering, we identified two main clusters, which projected to mutually exclusive targets and possessed distinct morphological features. Cluster 1 (C1) contained 177 reconstructed axons terminating in the median eminence (ME) and with few collaterals terminating within hypothalamic regions. Cluster 2 (C2), comprising of 87 neurons, in contrast, projected extensively throughout the brain. Some subtypes identified by our morphological characterization fitted neatly with previously described OXT functions. We also analyzed soma and dendritic morphological characteristics of PVH OXT neurons. Our single-neuron resolution observations provide comprehensive analysis of PVH OXT morphology and lay structural foundation for better understanding of the complex physiological function of OXT neurons.

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Poster

PSTR308. Connectomics: Central Nervous System

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.12/XX5

Topic: I.03. Anatomical Methods

Support: NIGMS: R35GM142566

Title: Mapping whole-brain activity in adult zebrafish by combining in-situ hybridization chain reaction with the adult zebrafish brain atlas and BrainGlobe

Authors: *N. RAJPUT, M. WONG, D. KANANI, A. SQUIRES, K. KUSH PARIKH, K. FIELDS, J. W. KENNEY;
Biol. Sci., Wayne State Univ., Detroit, MI

Abstract: Both adult and larval zebrafish have been increasingly used to study a variety of behaviors given their low cost, amenability to genetic manipulation, and genetic similarity to mammals. Adult animals are of particular interest because of their extensive behavioral repertoire; however, unlike larval animals, we lack the tools for mapping whole-brain activity mapping in adults. To map brain activity in adults we developed a method that combines *in situ* hybridization chain reaction (HCR) to detect the expression of the immediate early gene *c-fos*, with a tissue clearing technique, iDISCO+. Whole brains are then imaged using light sheet microscopy. To identify *c-fos* positive cells, we used CellFinder, a deep learning approach to cell identification that is incorporated into the BrainGlobe computational environment. Images were then registered to our recently created adult zebrafish brain atlas (AZBA) using advanced normalization tools (ANTs). We have successfully trained CellFinder to detect *c-fos* positive cells with high accuracy (96%) and found that *c-fos* expression peaks at 15-30 minutes following exposure to a novel tank. Utilizing this approach, we have begun to identify the neural mechanisms that underly exploratory behavior of adult zebrafish.

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Poster

PSTR308. Connectomics: Central Nervous System

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Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR308.13/XX6

Topic: I.03. Anatomical Methods

Support: Banco Santander-UCM PR44/21-29909

Title: The synaptome of the human insular cortex

Authors: N. CANO-ASTORGA[1,3,4], S. PLAZA-ALONSO[1,3], J. GONZÁLEZ-SORIANO[5], P. PÉREZ-LLORET[5], C. ROJO[5], I. SANTOS-ÁLVAREZ[5], J. DEFELIPE[2], ***L. BLAZQUEZ-LLORCA**[5];
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Abstract: The human insular cortex is considered the “fifth lobe” of the brain. Although it comprises less than 2% of the total cortical surface area it plays a crucial role in numerous functions. Previous in vivo neuroimaging studies in humans have identified three distinct functional subdivisions in the insular cortex: the dorsal anterior, ventral anterior, and posterior insula. These three regions exhibit different cytoarchitectonic characteristics. The anterior aspects of the insula are involved in the integration of complex autonomic, cognitive, and

emotional process, which are believed be important in interoceptive awareness. On the other hand, the posterior aspects are essential for integrating autonomic and interoceptive signals. However, the synaptic organization of this brain region is still unknown due to the challenges involved in studying the human brain. The current study focuses on analyzing the synaptic organization of the neuropil of layer III of these three different regions of the insular cortex: the agranular (anteroventral), dysgranular (anterodorsal) and granular (posterior) insular cortices. Human brain samples obtained from autopsies with short postmortem intervals (less than 3 hours) were utilized, and synaptic circuits were examined in 3D using Focused Ion Beam milling/Scanning Electron Microscopy (FIB/SEM). A specific software tool was employed to analyze synaptic density, morphometric characteristics, postsynaptic targets, and spatial distribution of the synapses. Preliminary results indicate that certain aspects of the synaptic organization are rather homogeneous, while others exhibit specific variations across the three insular cortices (such as the distribution of postsynaptic targets). This specific synaptic organization in these three brain regions could represent an anatomical basis of their distinct functions.

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Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.01/Web Only

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH ORIP 5R44OD031437-02
NIH NCI 1R44CA268728-01A1
USC Coulter Translational Research

Title: Development of implantable 3mL micropump for preclinical and clinical applications, including controlled metronomic chemotherapy for brain cancers

Authors: *T. HOANG[1], S. LEE[1], E. MENG[2];
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Abstract: Fluid Synchrony is developing a 3mL implantable drug delivery system for preclinical and clinical applications. For preclinical studies, the system will aid the discovery of new treatments and vaccines as well as drug-based neuromodulation therapies. Our microinfusion system consists of an implantable micropump, an external wireless programmer, and programmable dosing software. Newly-developed capabilities include a medical-grade primary battery and a programmable system-on-chip with Bluetooth telemetry transceiver, processor and memory. This automated microinfusion system will ultimately result in increased productivity

and reduced researcher exposure to potentially toxic drugs and disease vectors.
One specific clinical application that would greatly benefit would be for delivering chemotherapeutic drugs to the central nervous system (CNS) for the treatment of primary malignant and disseminated brain cancers. The blood-brain barrier (BBB) limits diffusion of high doses of systemic drugs into the cerebrospinal fluid (CSF). For those drugs that do cross the BBB, rapid CSF turnover reduces drug concentration in a matter of hours. The standard of care treatment results in CSF drug concentrations at initially toxic levels, which drop through the therapeutic window, then become sub-therapeutic. As a result of the limited efficacy of the standard of care, the CSF serves as a sanctuary for circulating tumor cells which disseminate in the CSF and form tumors on the leptomeninges. By using low concentration, tolerable, metronomic dosing regimen to increase AUC (Area Under the Curve), efficacy and outcomes may be significantly improved while reducing toxic side effects.The micropump fulfills an unmet need in brain cancer treatment, especially in pediatric applications where off-label use of adult pumps are not practical and not efficacious.
We present current progress on the development of the implantable micropump with 3mL drug reservoir. We will demonstrate a unique dual-needle fluid injection mechanism for percutaneous refill of the implanted micropump using negative-pressure syringe pull operation to avoid adverse pocket-fill events that plague other refill procedures for implanted infusion pumps.

Disclosures: **T. Hoang:** A. Employment/Salary (full or part-time):; Fluid Synchrony, LLC, Senseer Health Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fluid Synchrony, LLC, Senseer Health Inc. **S. Lee:** A. Employment/Salary (full or part-time):; Senseer Health Inc, Fluid Synchrony, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Senseer Health Inc. **E. Meng:** A. Employment/Salary (full or part-time):; University of Southern California, Fluid Synchrony, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fluid Synchrony, LLC, Senseer Health Inc.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.02/XX7

Topic: I.08. Methods to Modulate Neural Activity

Support: R01AG058814

Title: A urethane anesthesia protocol for robust recordings of bladder cystometrogram and visceromotor responses to bladder distention in mice

Authors: *E. WOON[1,2], S. ZHANG[1], L. CHEN[1], G. KUCHEL[2], B. FENG[1];
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Abstract: Bladder-related disorders, such as underactive or overactive bladder and chronic pelvic pain syndromes, are poorly managed in clinics, necessitating further mechanistic understanding of the underlying urodynamics and nociceptive neural circuitry. These disorders are usually studied through cystometrogram (CMG) and visceromotor responses (VMR) to urinary bladder distension (UBD) recorded in rats under urethane anesthesia. Here, we optimized a urethane anesthesia protocol to enable robust recordings of CMG and VMR in mice, offering a wider selection of disease models with the ease of genetic manipulations. Additionally, we assessed our anesthesia protocol on aged mice (18-22 months old), enabling geriatric studies on bladder-related disorders. In this study, C57BL/6 mice of both sexes were used: mature adults (10-12 months) and aged adults (18-22 months). Mice were first anesthetized with 1.75% isoflurane inhalation. A polyurethane (PE)-50 catheter was inserted into the dome of the bladder for delivering slow bladder filling (1.5 mL/hr) or stepped UBD (20, 40, 60, 80 cmH2O). Two stainless steel wire electrodes were sutured to the oblique abdominal muscles for recording the VMR. Another catheter was placed intraperitoneally (i.p.) for delivering urethane anesthesia. After the surgery, an initial dose of 0.6g/kg of urethane was administered, followed by a 30-minute period of reduced isoflurane to 0.25%. Then a 3-hour-long urethane infusion (0.15 g/kg/hr) was started. The micturition events were captured by measuring the urine weight with a force transducer. After establishing the baseline CMG and VMR, we assessed the effects of intravesical infusion of 0.5% acetic acid and 0.1% lidocaine on the CMG and VMR. Our anesthesia protocol, consisting of an initial dose of urethane and a 3-hour-long infusion, enabled robust CMG and VMR recordings for 3 hours in mice of both age groups. Intravesical acetic acid significantly enhanced the VMR to UBD and disrupted the regular micturition cycles in CMG, which were normalized by intravesical lidocaine. This new anesthesia protocol will enable focused studies to advance our mechanistic understanding of bladder-related disorders.

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Poster

PSTR309. Physiological Methods

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Program #/Poster #: PSTR309.03/XX8

Topic: I.08. Methods to Modulate Neural Activity

Support: BBSRC Grant BB/V000411/1

Title: Refining the use of general anaesthesia in embryo larval zebrafish: effective and tolerated concentrations of six commonly used fish anaesthetics

Authors: *S. DIMITRIADOU[1], M. C. M. MILLER[1], J. L. BAMSEY[1], D. HOGAN-BASSEY[1], A. PILEHVAR[1], A. RANDALL[1], A. TAKESONO[1], T. KUDOH[1], L. U. SNEDDON[2], M. J. WINTER[1], C. R. TYLER[1];
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Abstract: Zebrafish (*Danio rerio*) are one of the most widely used laboratory animals in scientific research worldwide, second only to the mouse in terms of regulated (invasive) procedures undertaken, for example, in the UK. Most experimental procedures are undertaken in the embryo-larval life stages, (typically <7 days-post-fertilisation or dpf), and many of these involve the use of anaesthesia, either as the first step towards euthanasia, or for procedures such as sedation for microscopic evaluation. Despite this, there is very little guidance available for humane and appropriate anaesthetic choices for fish, particularly for embryo-larvae. For example, limited research has been performed on establishing appropriate immersion concentrations (doses), lengths of induction and recovery times, or whether anaesthetic agents are poorly tolerated or aversive in embryo-larvae and as such may present a confounding factor. This knowledge gap has considerable implications both for the welfare of these animals, and for experimental design more widely. Our study used 4.5 dpf zebrafish embryos to explore the sedative and aversive characteristics of six of the most widely used fish anaesthetic agents: tricaine methanesulfonate, benzocaine, isoeugenol, 2-phenoxyethanol, quinaldine sulphate, and etomidate. The fully anaesthetic concentration for each agent was established by observing the effects of several different concentrations on heart rate, balance, and responsiveness to tactile stimuli, in addition to the induction and recovery times for each concentration/anaesthetic compound. Additionally, non-recoverable concentrations were established for each agent for application during euthanasia. Next, the aversive properties of each anaesthetic were assessed at a low (the highest concentration not causing anaesthesia) and a high (the highest concentration not eliminating heartbeat at recovery) concentration, using a novel behavioural avoidance test, combined with automated video analysis. Collectively, these studies revealed pronounced differences between the anaesthetic agents tested, both in their effectiveness and speed of induction, as well as in terms of their effect on the aversive behaviour of the larvae. Our findings indicate that certain anaesthetics are more effective and/or less aversive to zebrafish embryo-larvae and may, therefore, offer more ethical and scientifically appropriate alternatives in experimental procedures involving these widely used laboratory animals.

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Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.04/XX9

Topic: I.08. Methods to Modulate Neural Activity

Title: An optimized and versatile Small Molecule based Cell Supplement for stress reduction in Primary and PSC-Derived Neural Cell

Authors: *M. A. DERR[1], R. E. SCOTT[1], A. IBRAHIMI[1], J. TANCREDI[1], K. LAHA[2], S. SHIN[1];
[1]Thermo Fisher Scientific, Frederick, MD; [2]Thermofisher Scientific, Madison, WI

Abstract: Primary and pluripotent stem cell (PSC)-derived neural cell cultures are extensively utilized in neuroscience research to study basic neuronal function, development, morphology, disease modeling, drug development and neurotoxicity. However, the complex nature of these cells renders them particularly susceptible to the detrimental effects of stressful environments. In vitro workflows further exacerbate this vulnerability, potentially compromising experimental results and reducing the reliability of these models.Existing cell recovery supplements have shown improved survival in Pluripotent Stem Cells (PSCs), however, most are not recommended for neural cell applications and limited data is available. In this study, we aimed to address this issue by evaluating the efficacy of a small molecule based cell supplement (SMCS) in protecting neural cells from the stress induced during routine handling procedures such as recovery from the cryopreservation, dissociation and differentiation. To assess the versatility of SMCS, we included different neural cell types, namely primary neurons, PSC derived neurons and astrocytes. Our results demonstrate that SMCS can be widely employed to mitigate cell stress without compromising downstream applications. Furthermore, we conducted a comparative analysis to assess the performance of the SMCS in comparison to both the gold standard method specific to each application and a commonly used rho kinase inhibitor, which is a general reagent utilized for stress reduction. Remarkably, SMCS demonstrated superior performance, outperforming other compared reagents in terms of their protective capabilities.Overall, our study highlights the importance of addressing the vulnerability of primary and PSC-derived neural cell cultures to stress in order to enhance the reliability and utility of these models in neuroscience research. The introduction of the novel cell supplement, SMCS, provides a promising solution to protect these cells from the detrimental effects of routine laboratory manipulations, thus offering new opportunities for improved experimental outcomes and downstream applications.

Disclosures: **M.A. Derr:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **R.E. Scott:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **A. Ibrahimi:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **J. Tancredi:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **K. Laha:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **S. Shin:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific.

Poster

PSTR309. Physiological Methods

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Topic: I.08. Methods to Modulate Neural Activity

Support: KGM4562323
KFW0512311

Title: Alternative test of fearful temperament in non human primate

Authors: *M. KIM;
Korea Res. Inst. of Biosci. and Biotech., Cheongju-si, Korea, Republic of

Abstract: Non-human primate is widely used experimental animals due to its high similarity with human beings. However, this high correspondence between human beings requires more sophisticated research design. Unlike the rodent, non-human primate has higher cognitive capability and even each has personality or temperament as human beings. Traditionally, Human Intruder Test measuring the duration of bodily freeze in response to stranger is used for fearful temperament. However this method would accompany interpretation error and providing stress to the animals. Thus, standardized and sensitive test to assess temperaments among non-human primate is critical for further behavioral experiments. Here, we conducted a rigorous behavioral baseline experiment to identify each monkey's temperament and confirm whether they are right for further behavioral experiments. We conducted a reinforcement task with three cynomolgus monkeys with Cambridge Neuropsychological Test Automated Battery (CANTAB) and observed regular behavior in single-housed manner. First, the motivational behavior with CANTAB is conducted two to three times per week with a total time of 17 days. This behavior test is for measuring behavioral activation in response to novel stimuli. In the touchscreen, a particular shape appears in the monitor and the monkey is asked to touch the shape to get a reward, and their response time is measured— A: 2.50s, B: 6.89s, C: 8.90s. Then we also measured the abnormal behaviors with the various criteria: rapid orientation and flight behavior, sudden startle, visual tracking (eye gazing of invisible objects), grooming and circling with the mean time and total number of behaviors. Particularly, we focused on the stereotypic behavior; circling, which considered as monkey's typical anxious behavior. The total number of circling behavior of each is as follows A: 7.25 B: 11.75C: 14.75 with the two hours each for four days with the behavior measurement tool; observerXT. Based upon the results, we decided to exclude monkey C for future behavioral experiments due to its greater fearful temperament. We propose this touch-screen based task and behavioral observation would be more sensitive method for assessing fearful temperament of laboratory non-human primate.

Disclosures: M. Kim: None.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.06/XX11

Topic: I.08. Methods to Modulate Neural Activity

Support: ZIAMH002619-30

Title: Comparison of viral vectors for retrograde transduction of dopaminergic neurons in rhesus monkey

Authors: *A. S. PLOTNIKOVA[1], W. LERCHNER[1], A. C. CUMMINS[1], L. SALHANI[1], B. J. RICHMOND[1], Z. M. KHALIQ[2], M. A. G. ELDRIDGE[1];
[1]Lab. of Neuropsychology, NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD; [2]NIH/ NINDS, Bethesda, MD

Abstract: Engineered viral vectors have been used to target the neuromodulatory systems of the brain, but a conspicuous obstacle is the inability of many retrogradely infecting viruses to transduce dopaminergic (DA) cells (Cushnie et al., 2020; Tervo et al., 2016). In a comparative analysis, we assess four viral vectors in their ability to drive expression in the somata of DA neurons of nonhuman primates (NHP) after injection into striatum. AAV2-retro and lentiviral vectors pseudotyped with rabies Fusion Glycoprotein B, C, and E (FuG-B2, FuG-C, and FuG-E) are viruses that have been engineered to confer retrograde transfection properties. A variant of AAV2, rAAV2-retro, is endowed with the ability to be internalized by axons, enhancing retrograde transfection (Tervo et al., 2016). FuG-B2 (‘HiRet’) transduces all brain cell types (glia and neurons), while FuG-C and FuG-E ('NeuRet') are neuron specific (Kato et al., 2020). To evaluate retrograde transduction of dopaminergic cells in the rhesus monkey, virus was targeted to striatum in stereotaxic surgeries. We injected between 70 and 150 µL (10 µL/site at a rate of 0.5 µL/min to 1.0 µL/min) unilaterally across three anterior-posterior levels of each NHP. Post-mortem immunohistochemistry was visualized with fluorescence and brightfield microscopy, and the transduction efficiency of the viral vectors in dopaminergic cells was quantified. Qualitative and quantitative analysis of the data revealed lentivirus-based vector, FuG-B2, produced robust retrograde transfection of DA cells, as evidenced by the neuronal co-expression of fluorescent reporter protein and tyrosine-hydroxylase (TH) antibody in substantia nigra. This finding is contrasted with the other three viral vectors, which do not transfect dopaminergic cells as efficiently. FuG-C expression was approximately two times lower than that of FuG-B2. FuG-E showed minimal expression, while AAV2-retro produced almost zero expression.

Disclosures: A.S. Plotnikova: None. **W. Lerchner:** None. **A.C. Cummins:** None. **L. Salhani:** None. **B.J. Richmond:** None. **Z.M. Khaliq:** None. **M.A.G. Eldridge:** None.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.07/XX12

Topic: I.08. Methods to Modulate Neural Activity

Support: Support from Department of Applied Physiology and Kinesiology

Title: Regional Specific Changes in Alpha Reactivity During Tonic Pain Stimulation

Authors: *Q. NGUYEN, J. PARK, R. HO, S. COOMBES;
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Abstract: Alpha Reactivity (AR), characterized by alterations in alpha power between eyes-open (EO) and eyes-closed (EC) states, reflects the functionality and adaptability of the brain's attention system amidst varying cognitive demands. The attenuation of alpha power during the transition from EC to EO resting states — a change from a less attentive to a more attentive state — is well established and thought to rely on the cholinergic system, but the impact of pain on this transition is not well understood. The goal of the current study was to determine whether tonic experimental pain impacts AR. We collected 128-channel high-density electroencephalography (HD-EEG) from a cohort of young healthy adults. Data was collected during 2.5-minute pseudo-randomized rest periods, that varied as a function of the presence/absence of a tonic pain eliciting stimulus and whether their eyes were open or closed. Bootstrap paired t-tests on globally averaged AR revealed no significant differences ($p = 0.07$) between resting (mean ± SD: 0.46 ± 0.54) and pain conditions (0.41 ± 0.54). However, pre-planned region of interest (ROI) analyses using FDR corrected bootstrap t-tests revealed a significant decrease in AR during tonic pain in the left and right frontal electrodes ($p < 0.05$), but not in left and right occipital electrodes ($p > 0.05$). Our observations show that there are regional specific changes in AR when an individual is experiencing tonic pain. Prolonged thermal stimulation diminishes the brain’s capacity to modulate from EC to EO resting conditions in frontal electrodes, consistent with the mu rhythm, but less so in occipital electrodes. Our findings are consistent with task-based EEG studies in chronic pain that show deficits in the modulation of power in response to task demands. Whether attenuated AR during resting states translates to individuals with chronic pain remains an open question.

Disclosures: Q. Nguyen: None. **J. Park:** None. **R. Ho:** None. **S. Coombes:** None.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.08/XX13

Topic: I.08. Methods to Modulate Neural Activity

Title: Attention modulates synesthetic V4 photism salience

Authors: *L. C. WILLIAMSON, S. A. BAILEY;
Psychology, Texas Lutheran Univ., Seguin, TX

Abstract: Synesthesia occurs when stimulation of one sensory system induces spontaneous experiences in two or more perceptual systems. Chromesthesia is a form of synesthesia wherein hearing music evokes visual sensations, or photisms. Prior literature does not indicate whether photisms are fixed or dynamic for a given inducer. Photisms may be linked to trauma flashbacks. Cortical region V4 is involved in processing visual stimulus features. Neuroscientists have been

inconsistent at measuring chromesthetic activation of brain tissue. There are no published data on synesthesia using functional near-infrared spectroscopy (fNIRS) to measure cortical oxygenation as an activity indicator. Non-synesthetes viewed greyscale and color versions of the same images, and fNIRS captured V4 activation for only the colored stimuli. A blindfolded chromesthete listened to music clips and rated photisms while being measured using fNIRS, and V4 oxygenation measurements corroborated consistent subjective ratings over six months. For the present study, a blindfolded, experimentally naïve chromesthete listened to six song clips over 18 trials. The participant was instructed to increase photisms for four of the clips, and to decrease photisms for two clips. The participant's V4 and frontal cortex were monitored using fNIRS. Photism ratings were recorded before and after the trials. The participant increased oxygenation in V4 for the four stimuli targeted for increase while forebrain remained inactive. For decrease trials, V4 remained mildly active but was coupled with markedly increased forebrain activation. The absolute values of the differences between the pre- and post-trial ratings for the two targeted decrease condition ratings were calculated and added to the associated pre-test values, permitting analysis using a correlated samples t-test. Results indicated statistically significant changes across the two ratings with all values having moved in the predicted directions. fNIRS instrumentation reliably captured chromesthetic V4 activity. Efforts to increase photisms with directed attention resulted in significant ratings changes and concomitant oxygenation changes in V4. Efforts to decrease photisms resulted in reported reduction in photisms, though fNIRS did not detect reductions in V4 activity. Increased activity away from V4 may be responsible for the sense that photisms were reduced. These results suggest that chromesthetes may be able to modulate their photisms through attention. This finding may hold promise for people with comorbid PTSD and chromesthesia.

Disclosures: L.C. Williamson: None. **S.A. Bailey:** None.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.09/XX14

Topic: I.08. Methods to Modulate Neural Activity

Support: R01NS107472

Title: A ST3DIO to Bridging the Gap between Cutting Edge Neural Networks and High Throughput Behavior Pipelines

Authors: *J. M. ROACH[1], I. A. WEAVER[1], S. S. X. LIM[1], J. H. WU[1], J. A. RAVENEL[2], A. CHOUDHURY[1], A. ANSHUMAN[1], S. SINGH[1], B. C. SHIELDS[1], T. W. DUNN[1], M. R. TADROSS[1];
[1]Biomed. Engin., [2]Neurobio., Duke Univ., Durham, NC

Abstract: Cutting edge neural networks have demonstrated a robust ability to track the 3D kinematic behavior of freely behaving marker less mice. This enhancement in feature detection has allowed researches to uncover novel correlations between neural mechanisms and kinematic behavior. However the application of these technologies has been stifled by the difficulty of their implementation within high throughput behavior analysis pipeline. The expertise required to implement these technologies often requires dedicated person to develop a multi-view open field arena, implement the required software packages, and maintain the system. Lack of standardization between arenas prevents standardization between behavioral analysis pipelines. To bridge the gap between recent advancements in neural networks and high throughput behavior pipelines we developed the ST3DIO (Singe-camera Tracking 3-D Integrated Open field) platform. We use both hardware and software solutions to reduce setup time and fully automate the prediction pipeline. IR lighting illuminates the behavior chamber, providing consistent lighting conditions across our 5 occlusion fields of view. Mirrors to reduce system complexity and spatial foot print. Highly controlled lighting and background ensure that imaging conditions and animal experience remain identical between arenas. This further aids in minimizing network training for separate arenas. The software platform we developed leverages the hardware to automate the pipeline. Acquisition is performed using a built in GUI started with a desktop icon. Our system is integrated into Dropbox to distribute local computational tasks such as camera calibration across the computers in the behavioral arenas. A decentralized handler automates the predictions pipeline by parsing the Drobox server to submit unfinished predictions. This handler automatically performs cloud based transfers from the cloud storage to University clusters, starts and manages predictions processes, and automates transfers back to a cloud storage. The ST3DIO platform aims to create a one click solution from acquisition to key point prediction. The solutions with software design were meant to allow for developers to work within the platform. Logic for handling predictions using different networks is being implemented to allow for a streamlined addition of new networks. We are implementing software to keep track of which recordings were predicted given network(s) in our current dataset of over 5000 recordings. We aim to develop a high resolution high throughput platform for characterizing of models of disease such Parkinson's and Levodopa induced dyskinesia.

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Poster

PSTR309. Physiological Methods

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Program #/Poster #: PSTR309.10/XX15

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant R61 HL159948
NSF Grant IIS-2123781

Title: Manipulating Matrigel Concentration to Enhance Neural Network Formation and Electrophysiological Characteristics with Mouse Cortical Neural Stem cell

Authors: *S. KANG[1], H. KONG[2];
[1]Univ. of Illinois, Urbana-Champaign, Urbana, IL; [2]Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Urbana, IL

Abstract: Manipulating Matrigel Concentration to Enhance Neural Network Formation and Electrophysiological Characteristics in Mouse Cortical Neural Stem Cells
In recent times, there has been growing interest in utilizing in vitro neural networks derived from neural stem cells (NSCs) for a variety of applications. However, there remains a need to develop neural networks with specific electrophysiological characteristics. The differentiation and neural network formation of NSCs are influenced by various factors, including the extracellular microenvironment and growth factors. Of these factors, the material properties of the microenvironment impact NSC differentiation and migration, leading to distinct electrophysiological characteristics. Therefore, our study aimed to investigate the effect of Matrigel concentration on neural network formation and electrophysiological activities using mouse cortical NSCs. We cultured mouse cortical NSCs in Matrigel at a seeding density of 0.5M cells/cm^2. The NSCs were then subjected to three weeks of differentiation using different concentrations of Matrigel: low concentration (LC) at 6mg/ml and high concentration (HC) at 10mg/ml. We measured the material properties of each condition, including diffusivity, storage modulus, and loss modulus, through FRAP analysis, frequency sweep, and strain sweep tests. Immunofluorescent images were captured to assess neural outgrowth and branching in both conditions, and neurons were reconstructed using IMARIS neural tracing. Additionally, calcium flux imaging was performed to examine neural activities, including calcium flux rises and synchronicity. The results showed that the LC condition exhibited higher neurite outgrowth, but lower branching compared to the HC condition. The mean neurite length was 95.59um for the LC condition and 66.72um for the HC condition ($p<0.05$). The HC condition displayed a greater number of Sholl intersections across a broader range of distances from the soma, indicating higher branching order. Furthermore, the calcium flux imaging revealed that the HC condition exhibited greater synchronicity of calcium flux, despite similar calcium flux rises. Our study supports the hypothesis that a higher concentration of Matrigel culture substrate accelerates neural branching and the formation of neural networks, leading to more synchronized intracellular calcium flux activities. Further investigations are currently underway to determine the extracellular microenvironment factors that can cooperate with chemical factors for the rapid and efficient fabrication of neural networks that closely mimic in vivo neural networks.

Disclosures: S. Kang: None. **H. Kong:** None.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

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Program #/Poster #: PSTR309.11/XX16

Topic: I.08. Methods to Modulate Neural Activity

Support: SNSF Grant No. 51NF40-205608
InnoSuisse (Grant No. 56599.1 IP-LS)
ERC Advanced Grant "neuroXscales" (Grant Agreement No. 694829)

Title: Neurons differentiate magnitude, location and loading rate of mechanical forces

Authors: *K. KASUBA[1], A. BUCCINO[3], J. BARTRAM[2], B. GAUB[4], S. KUMAR[5], S. RONCHI[5], S. GEISSLER[6], A. HIERLEMANN[4], D. J. MUELLER[4];
[1]Swiss Federal Inst. of Technol. Zurich, basel, Switzerland; [2]D-BSSE, Swiss Federal Inst. of Technol. Zurich, Basel, Switzerland; [3]Allen Inst. for Neural Dynamics, Seattle, WA; [4]ETH Zurich, basel, Switzerland; [6]Dept. of Biosystems Sci. and Engin., [5]ETH Zurich, Basel, Switzerland

Abstract: In past studies, we have shown that mammalian cortical and hippocampal cells respond to mechanical stimulation through shear stress and local indentation by exhibiting two distinct response types: transient and sustained. Transient responses resemble spontaneous neuronal activity, while sustained responses last several minutes. Micrometer-sized bead stimulations evoke transient responses at low forces/pressures and sustained responses at higher forces/pressures. Axons exhibit predominantly sustained responses, while dendrites respond transiently. A synchronized approach combining atomic force microscopy (AFM), microelectrode arrays (HD-MEA), and fluorescence microscopy enables precise mechanical characterization and stimulation of individual neurons, revealing that mechanical stiffness does not correlate with electrophysiological activity. Transient mechanical stimuli evoke action potentials propagating along neurons. Spontaneously active neurons exhibit functional resilience to static compression but modulation of firing rate with transient/repetitive compression. Molecular investigations highlight the role of viscoelastic parameters and membrane-cytoskeletal coupling in differential neuronal responses. These findings advance our understanding of mechanosensitivity in neurons and open avenues for further exploration.

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Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR309.12

Topic: C.03. Parkinson's Disease

Support: NIH Grant MH126178

Title: Homecage assessment of complex behavioral phenotypes in adolescent mice

Authors: *K. M. NAUTIYAL;
Dartmouth Col., Hanover, NH

Abstract: Adolescence is a complex period for neural development and behavioral maturation of reward-related phenotypes. It is also a high-risk period for the development of neuropsychiatric disorders, including those which involve impulsive and reward-related behavior. In rodents operant behavioral paradigms provide rich data sets which allow for the careful analysis of reward, impulsivity, motivation, and learning phenotypes that are of high interest during adolescence. However, there are major barriers to performing these studies with commercially available equipment in adolescent rodents. First, rodents are generally trained on task-specific paradigms for at least a month which is incompatible for assessment during a 2-3 week long adolescent period in mice. Additionally, appetitive paradigms usually require prolonged food restriction during training which is not ideal for the physical growth occurring during adolescence. In order to address these issues, we developed an Arduino-controlled automated homecage, inexpensive and open-source behavioral testing system. It allows for the implementation of most standard operant paradigms in the homecage of rodents in shorter time frames without food restriction, and with much less experimenter effort. All construction and code for the DIY Nautiyal Automated Modular Instrumental Conditioning (DIY-NAMIC) system are open source. We used this system to delineate the trajectory of adolescent development of impulsivity in mice with a focus on premature responding and delay discounting measures. Overall, the DIY-NAMIC system allows for the comprehensive assessment of adolescent behavior in mice across multi-faceted complex phenotypes and throughout the extent of adolescent development. This is important for the study of neural development and behavioral maturation during this important developmental period.

Disclosures: K.M. Nautiyal: None.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

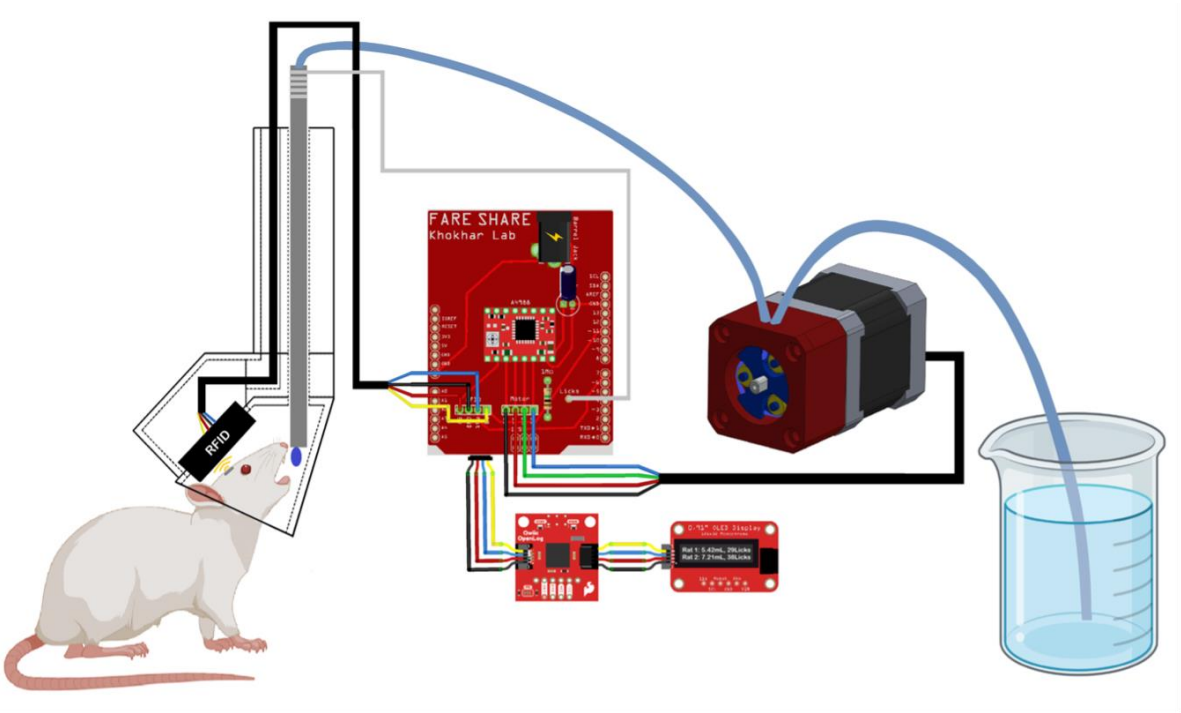
Program #/Poster #: PSTR309.13/XX17

Topic: C.03. Parkinson’s Disease

Title: An open-source device for measuring drinking microstructure in socially housed rats

Authors: *J. FRIE[1], J. Y. KHOKHAR[2];
[1]Biomed. Sci., Univ. of Guelph, Guelph, ON, Canada; [2]Anat. and Cell Biol., Western Univ., London, ON, Canada

Abstract:



Social factors have been shown to play a significant role in alcohol consumption. Studying the role of social context on alcohol drinking is important to understand the factors that contribute to initiation or maintenance of casual and problematic alcohol use. A large body of preclinical research has shown that social environment plays an important role in alcohol consumption and preference, though the extent of these effects have been obfuscated by methodological differences and technical challenges. Robust individual differences in alcohol intake in socially housed animals are difficult to track when animals share a common fluid source. Commercial solutions are prohibitively expensive and are limited by proprietary software and hardware. Here we describe an affordable, open-source solution for tracking fluid consumption in socially housed rats. The device uses RFID to identify rats, a lickometer to activate fluid delivery, a custom low-profile PCB that sits on top of an Arduino-based microcontroller, fluid delivery via custom peristaltic pump for accurate measurement of consumption volume, OLED display, and continuous data logging to an SD card. Here we validate our design via an alcohol two-bottle preference task. We use the data collected to determine fluid consumption, preference, and drinking microstructure of each of four rats housed in the same cage. Having a robust, affordable method for measuring drinking microstructure in socially housed animals will be of considerable use in preclinical addiction research and a step toward more translationally relevant animal models of fluid consumption. The added dimension of time allows for the analysis of circadian-linked consumption and the discrimination of continuous or binge-like drinking behaviours. Additionally, being open-source enables researchers to customize the device for more advanced applications such as sending signals to additional peripherals (e.g., optogenetic stimulation) or software on drinking initiation for time-locked or closed-loop interventions, manipulations, and measurements.

Disclosures: **J. Frie:** None. **J.Y. Khokhar:** None.

Poster

PSTR309. Physiological Methods

Location: WCC Halls A-C

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Program #/Poster #: PSTR309.14/XX18

Topic: E.05. Brain-Machine Interface

Support: Korea Health Industry Development Institute, HR21C0885

Title: Quantitative Balance Assessment with Wearable Pressure Insole in Patients with Brain Disorder

Authors: *W. CHANG, **J. LEE**, S. KIM, H. LEE, J. HWANG;
Samsung Med. Ctr., Seoul, Korea, Republic of

Abstract: Introduction: Gait impairment can induce the risk of falls and reduced quality of life among survivors of brain disorder. Predicting outcome of gait function is critical to the treatment of patients with brain disorder. Although balance is a known predictor of independence of gait, the best tools for balance evaluation in patients with brain disorder are still under debate. Wearable pressure insoles can effectively collect data during a variety of activities and the wireless communication technology provides much more data acquisition. The objective of this study was to investigate the feasibility of the wearable pressure insoles to assess balance function in patients with brain disorder. **Methods:** We recruited total 48 patients with brain disorder (mean age 61.7±15.5 years, 14 females). NEUROGAIT Insole (SALTED Co., Ltd, Korea) was used for the balance assessment in this study. The coordinate system of the insoles was set up and used to calculate the center of plantar pressure (COP). Investigator guided each participant to perform functional reach test (FRT). The COP displacement and the shift speed of COP were calculated for analysis. The experiment should be repeated at least three times, the plantar pressure data of each experimental subject was recorded and the maximum COP displacement was taken as the analysis data. Trunk control test (TCT) was also performed in each participant to assess balance function. The feasibility of the proposed method with wearable pressure insoles was verified by comparing with the results obtained using the FRT and TCT. **Results:** There was no significant adverse effect such as falls during balance assessments. The pressure change curve was acquired from characteristic points of the insoles during FRT in all participants. Each parameter such as COP displacement in wearable pressure insoles was significantly correlated with FRT ($p<0.05$). However, there was no significantly correlation between parameters in wearable pressure insoles and TCT. **Conclusion:** These results demonstrated that the wearable pressure insoles might be used for quantitative balance assessment in patients with brain disorder. Further study with larger number of patients will be needed to clarify the useful additional balance assessment tool of the wearable pressure insoles in this study.

Disclosures: W. Chang: None. **J. Lee:** None. **S. Kim:** None. **H. Lee:** None. **J. Hwang:** None.

Poster

PSTR309. Physiological Methods

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Program #/Poster #: PSTR309.15/XX19

Topic: I.08. Methods to Modulate Neural Activity

Support: Naval Information Warfare Center (NIWC) and the Defense Advanced Research Projects Agency (DARPA) Contract No. N65236-19-C-8013

Title: Application of Focused Ultrasound to Macaque FEF Prior to Onset of Saccade Cue Elicits Neural Changes

Authors: *R. HAMPSON[1], M. R. RILEY[1], B. M. ROEDER[1], M. P. WEISAND[2], G. F. PINTON[3], A. O. BILIROGLU[3], F. Y. YAMANER[3], O. ORALKAN[3], P. M. CONNOLLY[2]; [1]Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [2]Teledyne Scientific & Imaging, Research Triangle Park, NC; [3]NC State Univ., Raleigh, NC

Abstract: Low-intensity transcranial focused ultrasound (TFUS) is a promising method for non-invasive stimulation of brain tissue. TFUS has been used for neural stimulation in rodent, non-human primate, and human subjects. Herein we demonstrate TFUS stimulation that produces modulation of brain activity in the frontal eye field (FEF) while a macaque is performing a center-out task in which gaze fixation is followed by saccades to a left or right target.
In brief, we utilized a stationary transducer that provided 2.8 MHz pulsed TFUS to the FEF for 200 ms from a phased array of 4096 transducer elements. To dissociate TFUS-elicited and behavior-elicited neural signals, we stimulated 116 ms prior to a cue for the subject to saccade towards a left or right target. Local field potentials were recorded with multi-channel electrodes in FEF during task performance with sham or active stimulation.
Most importantly, we noticed that stimulation produced a sharp deviation of LFP signal as soon as stimulation started resulting in a higher level of activity following the saccade cue compared to non-stimulated trials. We were able to note that the signal reversed mid-way through the electrode shank, indicative that the stimulation-elicited neural activity was located near the FEF target and mid-way along the electrode shank. The neural activation was not observed when we stimulated with an air gap between the transducer and the surface of scalp or in sham trials.
These results indicate that TFUS stimulation can alter neural activity in a behaving primate. Additional work is underway to refine the parameters that are most effective in utilizing TFUS to influence neural signaling.
This work was supported by the Naval Information Warfare Center (NIWC) and the Defense Advanced Research Projects Agency (DARPA) under Contract No. N65236-19-C-8013. The views, opinions, and/or findings contained in this abstract are those of the author and should not be interpreted as representing the official views or policies, either expressed or implied, of the NIWC Atlantic, DARPA, or the Department of Defense.

Disclosures: R. Hampson: None. **M.R. Riley:** None. **B.M. Roeder:** None. **M.P. Weisand:** None. **G.F. Pinton:** None. **A.O. Biliroglu:** None. **F.Y. Yamaner:** None. **O. Oralkan:** None. **P.M. Connolly:** None.

Poster

PSTR309. Physiological Methods

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Program #/Poster #: PSTR309.16/XX20

Topic: I.08. Methods to Modulate Neural Activity

Support: Naval Information Warfare Center (NIWC) and the Defense Advanced Research Projects Agency (DARPA) Contract No. N65236-19-C-8013

Title: Applying Focused Ultrasound Stimulation Prior to Saccade Elicits Changes in Behavior

Authors: *M. RILEY[1], B. ROEDER[1], M. P. WEISAND[2], G. F. PINTON[3], A. O. BILIROGLU[3], F. Y. YAMANER[3], O. ORALKAN[3], R. HAMPSON[1], P. M. CONNOLLY[2]; [1]Wake Forest Univ. Sch. of Med., Winston Salem, NC; [2]Teledyne Scientfic & Imaging, Research Triangle Park, NC; [3]NC State Univ., Raleigh, NC

Abstract: Inducing a behavioral changes through activation of neural tissue is a key element in researching functions of brain regions. Brain activity in specific regions can be done invasively, for example, with electrode implantation or injected chemicals or viruses. We investigated the use of transcranial focused ultrasound (TFUS) to non-invasively stimulate brain regions. However, there remain many questions revolving around the properties of TFUS stimulation to influence behavior. Here, we report TFUS-elicited changes in a behaving nonhuman primate.
We delivered TFUS to the right frontal eye field (FEF) of a macaque performing a task requiring central gaze fixation followed by saccades to peripheral visual targets. In brief, we delivered 2.8 MHz pulsed TFUS to the FEF for 200 ms from a phased array of 4096 transducer elements. TFUS was targeted with phase delays calculated to correct for inhomogeneities from scalp, skull, and brain between transducer and the FEF target. TFUS was applied during central gaze fixation, 116 ms prior to the cue indicating the subject should saccade to left or right visual target locations.
We observed that TFUS induced a leftward bias of saccades compared to no stimulation trials. With stimulation nearly 10% more first saccades were leftward when the correct target was on the right side. In addition, there was a decrease in errant saccades toward the right target when the correct target was on the left. Finally, the median timing of saccades was slower in the stimulation condition compared to the non-stimulated trials.
Our results show that TFUS in our center-out task biased the saccade direction and the timing of the saccade. Additional work is underway to refine the parameters that are most efficacious in using TFUS to influence behavior.
This work was supported by the Naval Information Warfare Center (NIWC) and the Defense Advanced Research Projects Agency (DARPA) under Contract No. N65236-19-C-8013. The views, opinions, and/or findings contained in this abstract are those of the author and should not be interpreted as representing the official views or policies, either expressed or implied, of the NIWC Atlantic, DARPA, or the Department of Defense

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Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.01/XX21

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: A cascade of binding and cell-based assays designed to characterize 5HT2A receptor ligands and aid the investigation of signaling pathway bias

Authors: *D. DALRYMPLE, L. GERRARD, J. KEWNEY, R. PRIHANDOKO, E. PARKER, G. CHAN, G. VREME, D. SMITH, I. MCPHEE;
SB Drug Discovery, Glasgow, United Kingdom

Abstract: Serotonergic psychedelics are substances which possess the ability to alter mood, perception and thought processes, with the serotonin (5-HT) 2A receptor subtype as their main pharmacological target. Psychedelics have been increasingly recognized for their potential therapeutic benefit however their investigation has been hampered due to possible adverse side effects such as disorientation, anxiety, hallucinations, seizures and even death.
5HT2A receptors have been proposed to signal via multiple intracellular signaling cascades, including the canonical Gαq-coupled pathway, resulting in calcium release from intracellular stores, and the β-arrestin pathway resulting in receptor internalization and desensitization as well as downstream signal transmission.
It has been suggested that ligands showing bias towards specific signaling pathways may allow separation of the desired therapeutic effect from any undesired side effects and offer the potential to develop effective ligands that can be used to target specific neuropathological conditions. A clearer understanding of the molecular mechanisms of 5HT2A ligands would help contribute to the development of therapeutic psychedelic-like compounds. To enable this, we have developed a cascade of in vitro binding and cell-based assays designed to identify and characterize 5HT2A receptor ligands in detail, allowing interrogation of receptor subtype selectivity and signaling pathway bias.
Cell-based assays measuring calcium mobilization, β-arrestin interaction, receptor internalization and pERK levels were developed and validated using a selection of standard reference compounds including psychedelic and non-psychedelic ligands. This panel of cell-based assays provides the basis for assessing compound effects on different signaling pathways and aids the discovery of ligands with preferential signaling bias.

Disclosures: **D. Dalrymple:** None. **L. Gerrard:** None. **J. Kewney:** None. **R. Prihandoko:** None. **E. Parker:** None. **G. Chan:** None. **G. Vreme:** None. **D. Smith:** None. **I. McPhee:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.02/XX22

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Simultaneous spatial evaluation of IDH1, EGFR, IGF1R and Ki67 biomarkers in glioblastoma

Authors: A. OLIVER, J. HAGEN, K. TRUEMAN, G. LELAND, ***A. KALYUZHNY**; Bio-Techne, Minneapolis, MN

Abstract: Each year about 14,000 people in the United States are diagnosed with glioblastoma (GBM), the most aggressive primary neuroepithelial tumor. Patients with GBM have a poor prognosis and only 5% of these patients can survive for more than 5 years. Various biomarkers are used for Immunohistochemical (IHC) diagnosis of GBM including: Isocitrate dehydrogenase 1 (IDH1), Epidermal Growth Factor Receptor (EGFR), Insulin Like Growth Factor 1 Receptor (IGF1R), and a cell proliferating marker Ki67. Typically, IHC is done by using a single-biomarker HRP-DAB detection technique which is not suitable for the simultaneous spatial analysis of multiple biomarkers. The aim of this study was to develop a multi-color immunofluorescence protocol allowing for the spatial biology analysis of distribution and co-localization of biomarkers in GBM tissues. Paraffin-embedded tissue sections were incubated with a mixture of the following primary antibodies: monoclonal mouse anti-human IDH1 (MAB7049), polyclonal goat anti-human EGFR (AF231), monoclonal mouse anti-human IGF1R (MAB391), and monoclonal rabbit anti Ki67 (MAB7617). For detection, we used species specific secondary antibodies conjugated to fluorescent dyes with different excitation and emission spectra. At the qualitative level, we have observed about 80% of cells with strong immunoreactivity for EGFR and IDH-1 whereas IGF-1R labeling was confined to about 50% of cells. Immunoreactivity for Ki67 was the lowest and detected in about 5% of cells. About 80% and 50% of EGFR positive cells were also immunoreactive for IDH-1 and IGF-1R respectively. All Ki67 labeled cells were also immunoreactive for EGFGR and IDH1R but only 50% of Ki67 positive cells were immunoreactive for IGF1R. We applied a spatial biology methodology for co-detection of multiple GBM biomarkers which allowed us to analyze their spatial distribution as well as the extent of colocalization at the single-cell level. Co-detection of multiple biomarkers has a strong diagnostic potential especially when analyzing limited small-size biopsies.

Disclosures: A. Oliver: None. **J. Hagen:** None. **K. Trueman:** None. **G. Leland:** None. **A. Kalyuzhny:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.03/XX23

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: New Hampshire Network of Biomedical Research Excellence (NH-INBRE) Parent Grant Number: P20GM103506

Title: Overexpressed cytokines in cancer stem cells of rat and human glioma cells

Authors: *H. SHIN, L. NELSON, D. CASADO;
Rivier Univ., Nashua, MA

Abstract: Glioblastoma (GBM) is the most malignant and invasive brain cancer, and the average survival time of the patients is limited to 15 months, despite deep understanding of its genomic mutations and advanced medical therapeutics. Recent studies revealed that a unique subpopulation of cancer stem cells (CSCs) is the major cause of resistance to radiotherapy and chemotherapy and its recurrence of GBM. We aimed to compare differential cytokine expressions of the CSCs versus differentiated cancer cells. To this end, we employed the C6 rat glioma cell line and U251MG human glioma cell line due to their overall abilities to simulate the high growth rate, the high vascularization, and the highly infiltrative characteristics of GBM. We successfully isolated CSCs from the main population of the cell lines by utilizing conventional neurosphere assays, and properties of these CSCs were confirmed with immuno-fluorescence staining for a typical CSC marker, SOX2. The expression of SOX2 was observed only in CSC spheroids but not in the adherent differentiated cells. We harvested media of CSC-spheroids for the cytokine array on various dates. Repeated cytokine arrays detected several cytokines overexpressed in CSCs-spheroids as compared to adherent cancer cells. In the future study we will target those up-regulated cytokines with compounds to find potential therapeutics.

Disclosures: H. Shin: None. **L. Nelson:** None. **D. Casado:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.04/XX24

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Development and assessment of BBB-crossing capsids for enhanced gene delivery to the brain

Authors: *B. P. HEITHOFF, E. FIRNBERG, S. YOST, S. CHO, T. NGUYEN, A. MERCER, O. DANOS, J. SMITH;
Res. and Early Develop., REGENXBIO, Inc., Rockville, VA

Abstract: The blood-brain barrier (BBB) is responsible for the poor transduction of the brain by adeno-associated viruses (AAVs) following intravenous (IV) delivery, which is less invasive than intracranial parenchymal injections that require surgery. To improve brain transduction using the IV route, we and others have recently developed new capsids targeting specific BBB receptors to promote crossing. Here we present data on a novel approach fusing Designed Ankyrin Repeat Proteins (DARPins) to the AAV capsid to imbue affinity for BBB receptors. To better understand the BBB crossing capabilities of these vectors, we developed a battery of tests to assess biodistribution across different brain regions and cell-type specific transduction, used to initially characterize AAV9 and PHP.eB vectors at multiple doses (1e13, 5e13, 1e14, 2e14 GC/kg) in C57BL/6 mice after IV administration. Peripheral tissues and left-brain hemispheres were analyzed via ddPCR to quantify vector DNA and transgene transcripts (RNA). We measured the luminance of the fluorescent transgene in right brain hemispheres and immunohistochemistry to assess expression across different cells and neuronal subtypes. Biodistribution in brain for PHP.eB was found to peak at ~8 GC/cell at both medium and high doses (5e13 and 1e14 GC/kg), while AAV9 continued to increase at each dose level, reaching a maximum of ~2 GC/cell at the highest dose (2e14 GC/kg). Biodistribution in liver showed ten-fold lower vector DNA for PHP.eB compared to AAV9 at all doses. PHP.eB brains showed higher fluorescent luminance in all groups compared to AAV9. Histology for PHP.eB tropism in the brain revealed that expression was strongest in striatum, thalamus, and hippocampus, milder in cortex, and weakest in cerebellum. Conversely, AAV9 expressed best in cortex and brainstem, but weaker in subcortex. PHP.eB and AAV9 both targeted astrocytes in cortex. However, in striatum, thalamus, and hippocampus, PHP.eB primarily expressed in neurons, while AAV9 largely expressed in astrocytes. Neither capsid expressed in midbrain dopamine neurons. These *in vivo* experiments show the current capabilities and limitations of targeting the brain via the BBB. To develop a novel therapeutic vehicle, we created our own BBB-crossing capsids fused with DARPins that have strong affinity to different receptors enriched in BBB vessels. Initial *in vitro* studies with our first generation capsids show up to 38-fold higher transduction of receptor-expressing cells compared to AAV9 and are viable in terms of manufacturing. These pilot data demonstrate the utility of this approach in generating a novel class of BBB-crossing capsids with therapeutic relevance.

Disclosures: B.P. Heithoff: A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **E. Firnberg:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **S. Yost:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **S. Cho:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **T. Nguyen:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **A. Mercer:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **O. Danos:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **J. Smith:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc..

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.05/XX25

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Whole-brain quantitative 3D imaging of robot-assisted intracerebral AAV delivery: A Light sheet fluorescence microscopy study in mice

Authors: *T. TOPILKO, A. PARKA, F. L. SØRENSEN, J. PERENS, C. G. SALINAS, A. H. R. THOMSEN, J. HECKSHER-SØRENSEN;
Gubra, Hørsholm, Denmark

Abstract: Gene therapy using adeno-associated virus (AAV) as a vector has emerged as a novel therapeutic modality that has the potential to improve outcomes of diseases with currently no effective interventions significantly. Adeno-associated viruses (AAVs) have emerged as powerful tools for targeted gene delivery in various diseases, including CNS disorders. Various AAV serotypes have been identified, each exhibiting distinct transduction efficiencies and cell tropism. Researchers can achieve targeted and efficient transgene expression in a desired cellular population by selecting the appropriate AAV serotype. In combination with AAV delivery of Cre recombinase, this genetic strategy enables the visualization of cells with high precision and intensity. Light sheet fluorescence microscopy (LSFM), together with tissue clearing, have revolutionized the field of neuroimaging by enabling 3D imaging of intact biological specimens at cellular resolution. One of the primary advantages of LSFM imaging is its ability to provide an unbiased sampling of viral transfection throughout the brain. Here, AAVs (AAV9-CAG-eGFP, AAV9-hSyn-Cre-eGFP) were characterized in wildtype and Cre-tdTomato mice as visualized and quantified by LSFM coupled with deep learning computational analysis. To minimize human error and improve consistency, we used precise injections of AAVs, using the Neurostar stereotaxic robot, enabling precise injection of AAVs to CNS anatomical targets typically used in gene therapy (i.e., the ventricular system, hippocampus, entorhinal cortex, substantia nigra). We found that intracerebroventricular AAV injections resulted in widespread transfection of cells, notably in cerebellar Purkinje cells. On the contrary, intraparenchymal AAV injections labeled a local population of cells around the injection site. By harnessing the advantages of combined LSFM imaging-deep learning, we demonstrate how this unique pipeline enables whole-brain high-resolution visualization and quantification of fluorescently-labeled cells and AAV transduction patterns in preclinical gene therapy development.

Disclosures: **T. Topilko:** A. Employment/Salary (full or part-time):; Gubra, Hørsholm, Denmark. **A. Parka:** A. Employment/Salary (full or part-time):; Gubra, Hørsholm, Denmark. **F.L. Sørensen:** A. Employment/Salary (full or part-time):; Gubra, Hørsholm, Denmark. **J. Perens:** A. Employment/Salary (full or part-time):; Gubra, Hørsholm, Denmark. **C.G. Salinas:** A. Employment/Salary (full or part-time):; Gubra, Hørsholm, Denmark. **A.H.R. Thomsen:** A. Employment/Salary (full or part-time):; Gubra, Hørsholm, Denmark. **J. Hecksher-Sørensen:** A. Employment/Salary (full or part-time):; Gubra, Hørsholm, Denmark. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gubra, Hørsholm, Denmark.

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PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.06/XX26

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Design of an IQSEC2 minigene for AAV gene therapy

Authors: *A. LEVY[1], **V. BORISOV**[1], N. LEVY[1], M. SHOKHEN[2];
[1]Technion Israel Inst. of Technol., Haifa, Israel; [2]Bar Ilan, Tel Aviv, Israel

Abstract: Mutations in *IQSEC2* account for ~2-5% of children presenting with seizures, severe intellectual disability and ASD. Adeno-associated virus (AAV) is a promising means to perform gene therapy for CNS genetic disorders. However, a major limitation of AAV is the size of the gene that can be used. The *IQSEC2* open reading frame (ORF) far exceeds these limits. In order to design a reduced IQSEC2 ORF we modeled the wild type (WT) IQSEC2 protein and how its Sec 7 catalytic activity for ARF6 is allosterically regulated by the binding of apocalmodulin (ApoCM) to the IQ domain of IQSEC2. A structural model of IQSEC2 was prepared using the RaptorX server combined with molecular dynamics (MD) simulations. Our model suggests that when apoCM is bound to the IQ region, the N-terminal coiled coil domain pivots around a glycine hinge to interact with the Sec7 region, thereby blocking the accessibility of the Sec7 region to ARF6 and inhibiting the Guanine nucleotide exchange factor (GEF) activity of IQSEC2. However, Ca+2 binding to ApoCM destabilizes its binding to the IQ region of IQSEC2. With apoCM no longer bound to IQSEC2 the N-terminal fragment pivots away from the Sec7 region allowing free access of the Sec7 region to ARF6 and activation of the GEF activity of IQSEC2. We identified two regions of IQSEC2, one between the N-terminal region and the IQ apoCM binding region, and another between the IQ apoCM binding region and the Sec7 coding domain, which were structurally disordered and for which no function is known. After deletion of these fragments, we connected the amino acids bordering the deleted region using short flexible glycine loops. We demonstrate using MD that the stability of this IQSEC2 miniprotein and the thermodynamic stability of its protein-protein interactions with Arf6, apoCM and PSD95 are identical to that of the WT IQSEC2 protein. Moreover, as with the WT IQSEC2 protein we observed that when apoCM was bound to the miniprotein the N-terminal region interacted with the Sec7 region. When apoCM dissociated from the miniprotein the N-terminal region pivoted away from the Sec7 domain, thus showing an identical molecular regulatory mechanism for both the minigene and the WT protein. Using the Lumier protein-protein binding assay, the association of the IQSEC2 miniprotein with itself, CM, PSD95 and IRSp53 was comparable to that of the WT IQSEC. Future studies will evaluate whether the IQSEC2 minigene delivered by an AAV will rescue mice with IQSEC2 mutations.

Disclosures: A. Levy: None. **V. Borisov:** None. **N. Levy:** None. **M. Shokhen:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

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Program #/Poster #: PSTR310.07/XX27

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH DP1 Pioneer (to V.G.)
Caltech Diversity Fellowship

Title: In utero systemic administration of engineered and natural rAAV serotypes reveals diverse expression profiles in fetal mouse brain.

Authors: *C. R. JACKSON[1], M. BORSOS[2], V. GRADINARU[3];
[1]Neurobio., [3]Biol. and Biol. Engin., [2]Caltech, Pasadena, CA

Abstract: In utero gene therapy (IUGT) holds promise for addressing disorders in the developing embryo and early intervention is particularly important for neurodevelopmental disorders. Recent technological advances have enabled genetic access to the mouse fetus as early as embryonic day 15 (E15), by injecting recombinant adeno-associated viruses (rAAVs) into the fetal circulation. rAAVs are well tolerated by the immature fetal immune system and their non-integrating cargo can be customized to deliver transgenes for functional protein expression, gene regulatory elements, and editing constructs. However, there are substantial challenges to overcome in enabling effective and safe genetic intervention during early developmental stages. Prenatal rAAV systemic delivery leads to ectopic organ transduction and low expression in the fetal brain, limiting the technology to treatment of multi-organ disease states. We set out to identify rAAV variants with reduced off-target organ transduction and develop delivery technologies for early systemic access using the developing mouse embryo as a model. To characterize genetic intervention at an even earlier developmental time point than previously reported, we used a delivery method for systemic access to the mouse embryo as early as embryonic day 12 (E12), when the fetus is roughly 30% the biomass of E15. We injected Ai14-TdTomato reporter mice with an AAV9 virus encoding a Cre-recombinase and eGFP linked by a P2A self-cleaving peptide, allowing us to identify cells that are currently transduced as well as those whose ancestors are transduced. E12 injected embryos when assessed at E18 showed broad neuronal coverage of the CNS and high expression in the periphery, when compared to E15 injected embryos. These results indicate that gene manipulation in the E12 embryo with rAAV has potential for high efficiency gene editing in the brain, but is lacking in organ specificity.To build a specialized toolbox for systemic delivery to the embryo brain, we compared the transduction profiles of seven rAAV capsids systemically injected into E15 mouse fetuses. In choosing capsids, we focused on a diverse array of natural serotypes, published brain-biased capsids, and unpublished capsids that have shown diverse transduction profiles. Using bulk DNA and RNA sequencing across tissues, we identified the rAAV capsids with the highest brain transduction and lowest ectopic organ expression to be used as a parent serotype in a capsid evolution library. Integrating capsid screening and gene regulatory elements with early systemic delivery can open the path to targeted, efficient, in utero gene therapy in mammalian disease models.

Disclosures: C.R. Jackson: None. **M. Borsos:** None. **V. Gradinaru:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.08/XX28

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: The Carl Marshall and Mildred Almen Reeves Foundation

Title: Single-cell-resolution optogenetics for vision restoration

Authors: *P. RAMAKRISHNA, O. A. SHEMESH;
Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Optogenetics has become a popular experimental strategy for vision restoration in blindness-causing retinal diseases, which result from either a loss of rods, cones or retinal pigment epithelium. However, conventional optogenetics has had limited success in achieving high-acuity vision restoration, with the acuity of vision restored in non-human primates only reaching up to 20/249. This is because conventional optogenetic molecules (opsins) were expressed in neurons that extensively overlapped surrounding neurons and led to significant cross-activation. This multicellular photo-stimulation translated to low-acuity vision restoration. To address this issue, we have developed novel opsins that enable single-cell-resolution optogenetics in the retina. By achieving single-cell optogenetic resolution, these molecules can potentially support an improved acuity of vision restoration for retinal diseases. These may include retinitis pigmentosa, macular degeneration, and diabetic retinopathy.

Disclosures: P. Ramakrishna: None. **O.A. Shemesh:** None.

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PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

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Program #/Poster #: PSTR310.09/XX29

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NSF SBIR Phase II 2136850

Title: Autohcs: automated ai-based scoring of dose-response high-content neuroprotectant screens.

Authors: *T. FINDLEY, H. DODKINS, J. DELANEY, I. GOLDBERG;
ViQi Inc, Santa Barbara, CA

Abstract: As the process of drug discovery scales rapidly, so does our ability to quickly and robustly identify novel neuroprotectants. These compounds have broad-reaching applications, namely the reduction or elimination of the degenerative effects of stroke, neurological disease, or medical treatments like chemotherapy. Such drug development increasingly depends on high-content compound screens where automation is the key to rapid, impactful discoveries. AutoHCS^{TM} is an AI-based system developed by ViQi Inc. that automatically detects and scores dose-dependent phenotypic responses to drugs in high-content screens. The only inputs to the analysis are images from any automated plate imager and a plate map specifying concentrations, replicates, and controls. Because the system does not depend on segmentation, it works non-parametrically with multichannel fluorescence, a combination of fluorescence and brightfield, or brightfield alone. With these inputs, AIs are trained by AutoHCS to score cellular responses to compound concentration within hours. Depending on researcher needs, results can include comparing phenotype across the dosages of each single compound, identifying the location of a compound in phenotypic space in relation to positive and negative controls, and mapping all compounds across phenotypic space in relation to one another. Among other pilot screens, AutoHCS was successfully run on a neuroprotectant screen provided by Anatomic Incorporated. Here, human induced pluripotent stem cell (hiPSC) derived sensory neurons were introduced to several compounds found in chemotherapy treatments that cause degeneration. Our analysis found that, when neurons were pretreated with the neural protectant SARM1 inhibitor DSRM-3716, the harmful phenotypes induced by these compounds were significantly lessened. This analysis from data upload to full report took less than a day. AutoHCS entirely determines its training parameters using experimental controls rather than user input, which eliminates subjective criteria selection that may bias phenotype scoring. This also makes it both user-friendly and extremely flexible to researcher needs. AutoHCS directly addresses the need for automation, objectivity, speed, and versatility in neuroprotectant research and development.

Disclosures: **T. Findley:** A. Employment/Salary (full or part-time):; ViQi Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ViQi Inc. **H. Dodkins:** A. Employment/Salary (full or part-time):; ViQi Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ViQi Inc. **J. Delaney:** A. Employment/Salary (full or part-time):; ViQi Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ViQi Inc. **I. Goldberg:** A. Employment/Salary (full or part-time):; ViQi Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ViQi Inc.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.10/XX30

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: 1RF1MH128969
U01MH114824

Title: Large-scale validation of open-source monoclonal antibodies geared toward generating a comprehensive whole brain 3D atlas of molecular targets

Authors: *K. THIRTAMARA, K. BOWYER, A. MALIK, V. SAXENA, A. SHIPMAN, J. XU, W. WANG, Z. WU;
Weill Cornell Med., New York, NY

Abstract: Lack of reliable and reproducible antibodies are a serious financial drain on research dollars in addition to wasted time and effort in generating unreliable and non-reproducible data. Only a subset of commercially available antibodies has been validated to recognize their intended targets. A large number of them are polyclonal antibodies that are not renewable to support desired reproducibility in large-scale and long-term applications. Monoclonal antibodies (mAb) on the other hand can offer more consistency and are also better suited for quantitative analysis. Furthermore, amino acid sequence of reliable mAbs can be defined and used to generate recombinant versions with the same epitope recognition regions, which in turn can lead to greater adoption, lowered costs and address ethical challenges of using animals in antibody production. Despite decades of community effort in producing and distributing mAb resources, their use is still limited by availability and lack of systemic validation in defined applications across different species. We are leading concerted effort to screen and validate mAb resources from both commercial vendors, as well as the libraries generated through partners (Addgene, NeuroMab, JHU/CDI) funded by National Institutes of Health, for robust immunolabeling application. Our goals are 3-fold. First, to generate a comprehensive and openly accessible mAb resource for the neuroscience community. Second, to extend the validation of these mAbs beyond mouse brain tissue and include both non-human primate and the human brain. Third, to scale the use of validated mAbs for whole mount labeling for both mouse and human tissue in order to generate a comprehensive 3D brain proteomic atlas cross species. 3D whole mount labeling on cleared brains (and other organs) presents a unique tool to study spatial distribution of different cell types as well as a platform to reliably perform quantitative marker analysis through the use of validated monoclonal antibodies. We have established a validation pipeline for immunolabeling compatible with advanced tissue clearing and labeling, and following initial validation screened over 100 antibodies on mouse and human brain samples from Addgene's collection of recombinant monoclonal antibodies. We have made this resource available on our own website (https://mab3d-atlas.com/) and shared it with our partners (Addgene) (https://www.addgene.org/antibodies/all/) complete with protocol information as well as high quality images. As we continue to screen more mAbs and curate the validated mAb 3D atlas, we aim to turn this into a comprehensive and open-source platform for the larger neuroscience community.

Disclosures: K. Thirtamara: None. **K. Bowyer:** None. **A. Malik:** None. **V. Saxena:** None. **A. Shipman:** None. **J. Xu:** None. **W. Wang:** None. **Z. Wu:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

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Program #/Poster #: PSTR310.11/XX31

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Development of robust iPSC platforms for accurate predictions of efficacy and toxicity of new treatment modalities early in the development pipeline

Authors: *J. KOEPKE;
Ncardia Services B.V., Leiden, Netherlands

Abstract: With the discovery of induced pluripotent stem cells (iPSCs) by Shinya Yamanaka in 2006, iPSCs have become a powerful tool for drug discovery. A new era of nucleotide-based therapeutics offer a huge potential to specifically modulate cellular pathways in ways not previously possible. One example of such modality are Antisense Oligonucleotides (ASOs). ASOs are single-stranded nucleotides designed to bind complementary RNA targets which leads to reduced protein expression trough either RNA cleavage, altering splicing or blockage of translation. To enable cost effective screening in patient derived iPSC cells for ASO candidate identification and validation, we developed and optimized a scalable protocol for the differentiation of iPSCs to cortical neurons in sufficient quantities to support the various stages of the drug discovery process. Furthermore, we established an high throughput in vitro assay in 384-well format to study the effects ASOs on target gene knockdown in a fully automated setting which allows for fast and cost-efficient selection of preclinical candidates. During assay development, we tested two RT-qPCR kits and selected one based on PCR performance: assay linearity and curve fit, target and normalizer amplification efficiency and feasibility of multiplexing. Automation of all steps of the assay enabled the development of a highly robust assay with inter-plate variation (%CV) between technical and biological replicates being less than 5% CV. With ASOs being increasingly used to treat central nervous systems (CNS) disorders, neuronal toxicity is of major concern, primarily driven by neuronal toxicity and/or neuroinflammation. A recent publication has demonstrated that ASO-induced reduction in frequency and amplitude of calcium spikes are predictive of in-vivo acute neurotoxicity [Hagedorn PH et al, Nucleic Acid Ther. 2022 Jun;32(3):151-162]. Being able to predict acute side effects early in the drug development process, not only facilitates the confident selection of candidates with higher chances of success in preclinical and clinical stages, it also supports lead optimization to reduce toxicity which overall saves time and resources. To further aid, prioritize and optimize drug candidates and we developed iPSC-CNS cultures (a co-culture of different neuronal subtypes and astrocytes) in which we established an in vitro assay in 384-well plate format to detect changes in calcium transients. In conclusion, we developed two custom assays using stem cell-derived neuronal cell models which support drug developers during their mission throughout various stages of drug development while reducing the use of laboratory animals.

Disclosures: **J. Koepke:** A. Employment/Salary (full or part-time):; Jessica Koepke, Kimberley Riegman, Benoit Samson-Couterie, Katerina Pitsa, Shushant Jain.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

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Program #/Poster #: PSTR310.12/XX32

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: ZIAMH002795
ZIAMH002793
ZIADA000069

Title: Discovery of PSG07 for chemogenetic research: a candidate ultrapotent PSAM^4 actuator and PET reporter probe

Authors: S. NERELLA[1], S. TELU[1], J.-S. LIOW[1], S. ZOGHBI[1], J. GOMEZ[2], M. MICHAELIDES[2], C. MAGNUS[3], S. STERNSON[3], B. RICHMOND[4], *M. ELDRIDGE[4], V. W. PIKE[1], R. B. INNIS[1];
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Abstract: Chemogenetic technologies with expression targeted to specific neuronal populations are emerging as potential treatments for neuropsychiatric and neurological disorders. Chemogenetic tools have been widely used to prove a causal link between specific neural circuits and behavior in small animals. To apply these techniques to non-human primates, however, post-mortem analysis has been required to evaluate the location and expression of constructs, making such work expensive and logistically difficult. PET imaging monitors the initial and longitudinal expression of chemogenetic receptors non-invasively. This type of monitoring could be very valuable for the application of gene-delivery techniques to long-term behavioral studies and in clinical settings. The 'PSAM-PSEM' system is an example of such a technology. Pharmacologically Selective Actuator Modules (PSAMs) are chimeric ligand-gated ion channels. They comprise a modified α7 nicotinic acetylcholine receptor (α7-nAChR) ligand-binding domain coupled to either an excitatory 5-HT$_3$ receptor (PSAM-5HT$_3$) or an inhibitory glycine receptor (PSAM-GlyR). Pharmacologically Selective Effector Molecules (PSEMs) are small-molecule agonists that are intended to bind selectively with PSAMs [1]. The triple mutant PSAM ($\alpha7^{L131G,Q139L,Y217F}$, denoted PSAM^4) can be activated with varenicline. However, varenicline binds endogenous receptor and is not selective solely for PSAM^4. Further optimization of varenicline's structure resulted in four ultrapotent Pharmacologically Selective Effector Molecules (uPSEMs) (*e.g.*, uPSEM792; K_i, 0.7 nM, [2]). uPSEM 792 is selective for PSAM^4-GlyR over other endogenous receptors, except α4β2 nAChR. We labeled uPSEM792 with carbon-11 ($t_{1/2}$ = 20.4 min) as a candidate radioligand for monitoring PSAM^4-GlyR expression in animals with PET. However, we found [^{11}C]uPSEM792 to be limited as a tracer by high polarity that likely reduced brain entry. Through a medicinal chemistry campaign based on uPSEM792 as lead, we discovered PSG07 as a much less polar PSEM but with high-affinity for PSAM^4-GlyR (K_i, 4.6 nM) and also amenable for labeling with fluorine-18 ($t_{1/2}$, 110 min). Voltage sensitive FLIPR dye assay showed PSG07 to be a PSAM^4-GlyR agonist with α7-nAChR/uPSAM selectivity comparable to that of uPSEM792. We prepared an iodonium ylide precursor of

PSG07 for ^{18}F-labeling and obtained [^{18}F]PSG-07 in useful yields. [^{18}F]PSG07 showed good brain uptake and 27% higher uptake of radioactivity at the target site in a PSAM^4-GlyR monkey. PSG07 shows potential as a brain-penetrant PSAM^4 actuator and [^{18}F]PSG-07 as a PET reporter probe, with further characterization in progress.

Disclosures: S. Nerella: None. **S. Telu:** None. **J. Liow:** None. **S. Zoghbi:** None. **J. Gomez:** None. **M. Michaelides:** None. **C. Magnus:** None. **S. Sternson:** None. **B. Richmond:** None. **M. Eldridge:** None. **V.W. Pike:** None. **R.B. Innis:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.13/XX33

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: A reproducible and quantitative capillary electrophoresis immunoassay for eNOS protein expression measurements directly in human brain tissue homogenates

Authors: P. JOSHI, F. RAMIREZ, **M. MILICI**, C. HAITJEMA, I. EUGENIS, *K. GARDNER, C. HEGER;
Bio-Techne, San Jose, CA

Abstract: Detailed proteomic characterization of human brain tissue is needed to identify potential novel biomarkers and drug targets for a variety of neurological diseases. The enzyme-linked immunosorbent assay (ELISA) offers quantitative protein expression measurements with high specificity and sensitivity. However, ELISA is challenged by brain tissue samples, which can have significant interference by matrix effects due to the high content of lipids and lipoproteins, as well as sheer protein intricacy that results from the brain's complexity. As a result, ELISAs for studying protein biomarkers of neurological diseases are limited primarily to peripheral blood and CSF samples.
Here, we developed a capillary electrophoresis immunoassay (CE immunoassay) for measuring a biomarker of the cerebrovascular system, eNOS, directly in human brain whole tissue homogenates. We show that the size-based separation provided by the CE immunoassay identified differential expression of eNOS isoforms in brain tissue compared to cultured endothelial and cervical cancer cells which could not be detected by ELISA. Compared to a commercial ELISA kit, the CE immunoassay demonstrated increased sensitivity and dynamic range of detection. Furthermore, differences in tissue homogenization and storage buffer conditions impacted the ability of ELISA to detect eNOS in brain tissue samples but had no observable effect on the CE immunoassay. Finally, the CE immunoassay consumed less brain tissue for analysis, needing only 3 µL of homogenate compared to 50 µL for ELISA. Because the CE immunoassay requires only one target-validated antibody for detection, we anticipate that the CE immunoassay will enable the analysis of additional protein biomarkers in brain tissue samples that historically have been challenging to detect by traditional ELISAs.

Disclosures: **P. Joshi:** A. Employment/Salary (full or part-time):; Bio-Techne. **F. Ramirez:** A. Employment/Salary (full or part-time):; Bio-Techne. **M. Milici:** A. Employment/Salary (full or part-time):; Bio-Techne. **C. Haitjema:** A. Employment/Salary (full or part-time):; Bio-Techne. **I. Eugenis:** A. Employment/Salary (full or part-time):; Bio-Techne. **K. Gardner:** A. Employment/Salary (full or part-time):; Bio-Techne. **C. Heger:** A. Employment/Salary (full or part-time):; Bio-Techne.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.14/XX34

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Internal research funding from Otsuka Pharmaceutical Co., Ltd.

Title: Phenotypic screening using waveform analysis of synchronized calcium oscillations in primary cortical cultures

Authors: ***R. SAKAGUCHI**[1], S. NAKAMURA[2], H. IHA[3], M. TANAKA[4];
[1]Dept. of Lead Discovery Research, New Drug Res. Div., Otsuka Pharmaceut. Co Ltd, Tokushima, Japan; [2]Dept. of Res. Management, New Drug Res. Div., [3]Office of Bioinformatics, Dept. of Drug Discovery Strategy, New Drug Res. Div., Otsuka Pharmaceut. Co., Ltd., Minoh-shi, Japan; [4]Dept. of Lead Discovery Research, New Drug Res. Div., Otsuka Pharmaceut. Co., Ltd., Tokushima, Japan

Abstract: At present, *in vitro* phenotypic screening methods are widely used for drug discovery. Fluorescence measurements of calcium oscillations in neurons are commonly used for measurement of neuronal activities, and some drugs have been evaluated using this assay technique. Here, we have developed a high-throughput screening system containing a new analysis method for quantifying waveforms, and our method has successfully enabled simultaneous measurement of calcium oscillations in a 96-well plate. Features of waveforms were extracted automatically and allowed the characterization of some anti-epileptic drugs using principal component analysis. Moreover, we have shown that trajectories in accordance with the concentrations of drugs in principal component analysis plots were unique to the mechanism of drugs. Finally, we successfully scaled up this method to 384-well plates to evaluate compounds which have other indications or mechanism of actions. We believe that an approach that focuses on the features of calcium oscillations will lead to better understanding of the characteristics of existing drugs and allow to predict the mechanism of actions of novel drug candidates.

Disclosures: **R. Sakaguchi:** A. Employment/Salary (full or part-time):; Otsuka Pharmaceutical Co., Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otsuka Pharmaceutical Co., Ltd. **S. Nakamura:** A. Employment/Salary (full or part-time):; Otsuka Pharmaceutical Co., Ltd.. E.

Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otsuka Pharmaceutical Co., Ltd. **H. Iha:** A. Employment/Salary (full or part-time):; Otsuka Pharmaceutical Co., Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otsuka Pharmaceutical Co., Ltd. **M. Tanaka:** A. Employment/Salary (full or part-time):; Otsuka Pharmaceutical Co., Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otsuka Pharmaceutical Co., Ltd..

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.15/XX35

Topic: I.06. Computation, Modeling, and Simulation

Title: Nu-Serum™: A superior media supplement for SH-SY5Y cell culture

Authors: *Z. B. KAYA[1], V. SANTIAGO-PADILLA[2], P. MCLEAN[1];
[1]Mayo Clin., Jacksonville, FL; [2]Univ. of Puerto Rico, San Juan, Puerto Rico

Abstract: Understanding the underlying mechanisms of neurological diseases is crucial for developing effective treatments and potential cures. Studies aimed at unraveling complex interactions between genetic, molecular, and environmental factors often focus on key pathological cellular processes with in vitro cell culture experiments playing a vital role in advancing our understanding of these diseases. Neuronal cell lines are invaluable tools because they can mimic the properties and behaviors of cells of neuronal origin. The SH-SY5Y human neuroblastoma cell line is one of the most widely used cellular models. SH-SY5Y cells can be differentiated into neurons and offer the advantage of studying impaired dopamine metabolism and other pathologies. However, these cells are extremely sensitive, and proliferation rates tend to be slow. Typical culture conditions involve DMEM F12 + 10% Fetal Bovine Serum (FBS). Herein, we performed a study to evaluate the utility of serum alternatives to test the hypothesis that an alternative serum supplement will aid and promote SH-SY5Y cell proliferation and differentiation when compared to traditional serum. Nu-Serum (NuS) is a low-protein alternative for newborn calf and fetal bovine sera. To compare the effect of NuS to FBS SH-SY5Y cells were cultured in DMEM F12 +10% FBS, DMEM F12 + 10% NuS, or serum-free (SF) conditions. Cell counting, cell size, and viability were evaluated by automated cell counter on days 2, 4, and 6 of culturing (n=6) and cell proliferation measurements were assessed by WST-1 assay on days 1 through 6 (n=8). Cells were observed under a brightfield microscope each day and imaged on days 2, 4, and 6. Cells were observed to develop neuron-like morphology faster in the NuS-treated group. Higher cell numbers were detected in the NuS-treated group, compared to the FBS-treated group (day 6 cell number $p=0.017$) and the SF-treated group (day 6 cell number $p<0.0001$). Both sera treated groups showed higher viability, but only NuS-treated group had significantly larger cell size compared SF-treated group. Cell proliferation was higher in the

NuS-treated group compared to FBS-treated ($p<0.0001$) and SF-treated groups ($p<0.0001$). Our data support NuS as a suitable serum alternative for SH-SY5Y cell culture. Overall, NuS offers an advantage with improved cell proliferation, viability, and morphology. Adjustments to cell culture protocols for this cell line may yield better cell health and positively influence the quality of research, especially in the neuroscience field.

Disclosures: **Z.B. Kaya:** None. **V. Santiago-Padilla:** None. **P. McLean:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.16/XX36

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Novel platforms to investigate Central Nervous System diseases for discovery purposes

Authors: M. BSIBSI[1], M. ZANELLA[1], B. TORROBA[1], M. DA SILVA[1], *L. RITSMA[1], D. MAGNANI[2], M. IOVINO[2], R. REDIS[1], M. HERVA MOYANO[2], L. BUTI[1], M. VLAMING[1]; [1]Charles River Lab., Leiden, Netherlands; [2]Charles River Lab., Saffron Walden, United Kingdom

Abstract: Robust, reproducible and upscalableplatforms to discover and develop disease modifiers for Central Nervous System(CNS) diseases, in high throughput formats, are urgently needed. In recentyears, significant advances in technology, particularly in the areas of 2D and3D stem cell research and gene/RNA editing, have translated into newopportunities to better understand brain diseases. Applying them within a drugdiscovery setting enables discovery of potential treatments on the mostrelevant cell models.Both induced pluripotent stem cells (iPSCs)and organoids represent promising resources for modeling CNS diseases. iPSCshave the ability to differentiate into various CNS cells and can be used togenerate patient-specific neurons or glial cells either as single cell typesor, with increasing complexity, in co-cultures. Organoids offer athree-dimensional representation of the brain, enabling the investigation ofCNS development and architecture, connectivity, and function; thus, allowing toclosely mimic in vivo conditions.Our recent results confirm thatiPSC-derived neurons and microglia are indeed a robust platform to studyneurodegenerative disorders, such as Amyotrophic lateral sclerosis (ALS) andAlzheimer's Disease (AD). First, we showed that these models possessphenotypical and functional properties similar to what observed in the humanbody, including electrical activity (neurons) and cytokine release (microglia).Next, we observed that some of these properties differed between healthy anddiseased cell lines and mimicked pathological conditions, for example a reducedneural firing activity in neurons with mutations in key ALS causative genes. Inaddition, we successfully applied the antisense oligonucleotide (ASO)technology in iPSC-derived neurons, by reducing the overexpression of genesresponsible for Dup15q Syndrome.Finally, we investigated the presence ofmultiple cell types (neurons, astrocytes, microglia and oligodendrocytes) in abrain 3D model, through immunostaining of canonical

markers and high resolutionconfocal imaging.Takentogether, these platforms and associated assays can help identify noveltherapeutic targets and improve our understanding of disease mechanisms, withthe ultimate goal of establishing effective treatments for CNS diseases.

Disclosures: **M. Bsibsi:** None. **M. Zanella:** None. **B. Torroba:** None. **M. da Silva:** None. **L. Ritsma:** None. **D. Magnani:** None. **M. Iovino:** None. **R. Redis:** None. **M. Herva Moyano:** None. **L. Buti:** None. **M. Vlaming:** None.

Poster

PSTR310. Molecular and Cellular Techniques for Discovery and Therapeutics

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR310.17/XX37

Topic: B.04. Synaptic Transmission

Title: A Web Application for Identifying Critical Protein Regions from Human Genetics Data

Authors: *A. W. LEHR, K. W. ROCHE;
Neurosci., NINDS, Bethesda, MD

Abstract: The increased availability of human genomic sequencing data has allowed for the association of genetic variations to disease. With large genetic heterogeneity in the human population, it is important to understand which residues/domains of human genes are tolerant or intolerant to variation. A disproportionate number of mutations in synaptic proteins have been implicated in neurological disorders such as autism spectrum disorder, schizophrenia, and epilepsy. Historically, neurological disease variant studies relied on finding patient mutations and characterizing how the mutation disrupted the protein (i.e., trafficking deficits, disrupting protein-protein interactions, and affecting post-translational modification sites). With a recent abundance of human genetic variant data, of both unaffected and neurologically impacted individuals, we can use low-powered statistics to determine critical regions of proteins and predict functional impacts of mutations.
We have developed a website that generates variant alignment graphics that display the location of variants in both unimpacted and impacted populations along a single protein domain map. Our program automatically pulls variants from ClinVar, an aggregated database of human genomic variants maintained by NCBI, as well as from gnomAD, an exome and genome sequencing database from unimpacted individuals maintained by the Broad Institute. These charts are then aligned to a functional domain map of the protein, allowing the user to map loci of variants along the protein alignment. Equipped with these data, we have developed an algorithm that compares loci of variants in unimpacted populations versus impacted populations, revealing protein regions that are significantly enriched with disease-associated variants and *in absentia* of unimpacted population variation. Users can enter a gene of interest and examine clusters of disease-associated variants and unimpacted-population variants to determine critical residues/regions/domains in the gene of interest to inform hypothesis generation. Additional filtering tools sort by disease, mutation type, and hetero/homo/hemizygosity to glean specific

insights into the impacts of various mutations. Our website is now publicly available at [comparagene.com].
With additional publicly available resources such as Protein Data Bank and AlphaFold providing models of protein structure, we can corroborate critical regions by comparing human genomic data to the protein structure, and even overlay deleterious mutations onto our structures to create predictive models of impacted protein structures.

Disclosures: **A.W. Lehr:** None. **K.W. Roche:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.01/Web Only

Topic: I.07. Data Analysis and Statistics

Support: NIH grant U01AG068057 to the AI4AD Initiative.

Title: Improved Alzheimer's Disease diagnosis with structural brain MRI using 3D deep learning architectures and knowledge transfer across domains

Authors: *N. DHINAGAR, A. SINGH, S. OZARKAR, K. BUWA, S. THOMOPOULOS, E. LALTOO, P. THOMPSON;
USC, Los Angeles, CA

Abstract: According to the Center for Disease Control and Prevention, 5.8 million people were living with Alzheimer’s disease (AD) in the U.S. alone during 2020 - a number expected to increase threefold by 2060. Artificial intelligence (AI) methods have recently shown vast progress for healthcare applications as well as neuroscience research. In this work, we demonstrate performance improvements in AD diagnosis based on 3D T1-weighted brain MRI scans (T1w), using novel 3D deep learning architectures pre-trained using diverse strategies known as transfer learning. We studied a total of 4,098 T1w from 1,188 participants in Alzheimer’s Disease Neuroimaging Initiative (ADNI) - ADNI1, GO, 2 - (55.7-92.8 years, 418F/461M) for AD classification; data was respectively split into 2577, 302, and 1,219 T1w for training, validation and testing sets, with unique subjects restricted to a specific fold, thus avoiding data leakage given repeat scans. We used 600 T1w (43.5-97.0 years, 341F/359M) from the Open Access Series of Imaging Studies (OASIS) as an out-of-distribution test dataset. The pre-training data included 38,703 T1w (44.58-82.75 years, 20,216F/18,487M) from the UK Biobank (UKBB), 100,000 (44-82 years, 50,123F/49,877M) synthetic T1w generated using a Latent Diffusion model (LDM) trained on UKBB and Kinetics-400, a publicly available dataset with 276,708 separate videos. The use of natural videos and synthetically generated data to pretrain 3D models are emerging transfer learning techniques to natively learn generic features for computer vision tasks based on large-scale data. For our experiments, we used the SwinT vision transformer, DenseNet121 convolutional neural network (CNN), MiNiT Transformer, and

Tiny-DenseNet CNN. The SwinT, MiNiT, TinyDenseNet and DenseNet121 trained from scratch respectively achieved test ROC-AUC of 0.8498, 0.8497, 0.8852, 0.8940 on ADNI, and 0.8327, 0.8130, 0.8348, 0.8158 on OASIS. The SwinT pre-trained on Kinetics-400 boosted the test ROC-AUC to 0.9235 (+7.4%) on ADNI and to 0.8501 (+1.7%) on OASIS. The DenseNet121 pre-trained on LDM, ADNI (self-pretraining), UKBB with contrastive learning weakly-supervised by age, achieved a test ROC-AUC of 0.8916, 0.9006 (+0.7%), and 0.9159 (+2.2%) on ADNI and test ROC-AUC of 0.8194 (+0.3%), 0.8175 (+0.2%), and 0.8409 (+2.5%) on OASIS, respectively. Our results show that pre-training with large scale datasets, i.e., UKBB for the DenseNet121 CNN and Kinetics-400 for the SwinT, yields an improvement in AD diagnostic accuracy. The pre-training pipelines proposed here could provide an initialization for training AI models for neuroimaging tasks with limited data and data heterogeneity.

Disclosures: **N. Dhinagar:** None. **A. Singh:** None. **S. Ozarkar:** None. **K. Buwa:** None. **S. Thomopoulos:** None. **E. Laltoo:** None. **P. Thompson:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.02/XX38

Topic: I.07. Data Analysis and Statistics

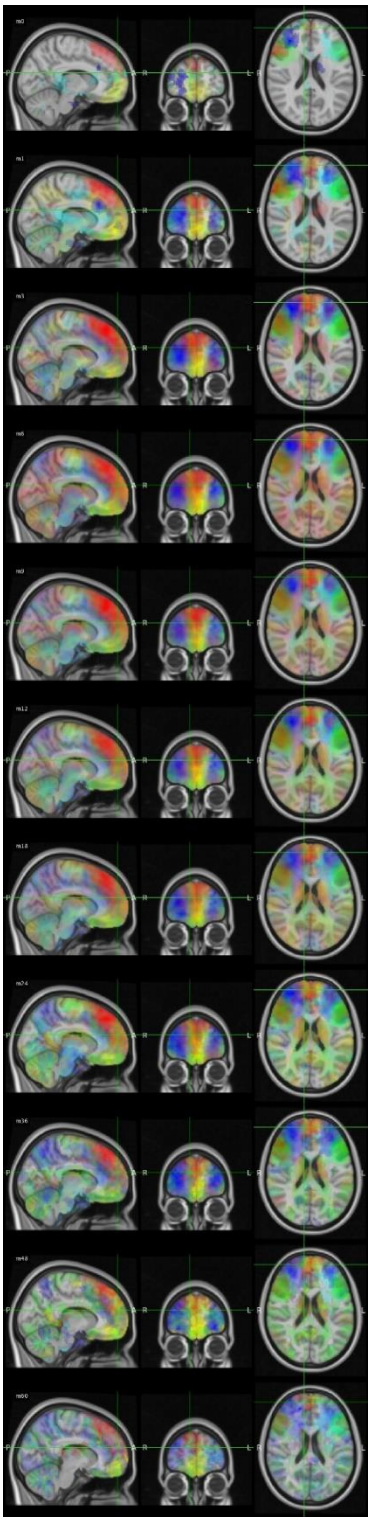
Support: NIH Grant R01MH125479
NIH Grant R01EB008374

Title: Emergence of Fronto-Cerebellar Connectivity During Infancy

Authors: W. LYU[1], K.-H. THUNG[1], L. WANG[1], W. LIN[1], S. AHMAD[1], ***P.-T. YAP**[2];
[1]Dept. of Radiology, [2]Univ. of North Carolina, Chapel Hill, NC

Abstract: Although the cerebellum is widely recognized for its involvement in motor and non-motor functions, the timing and extent of its involvement in motor and higher cognitive functions during early development remain unclear. Here, we show evidence of the emergence of fronto-cerebellar connectivity between birth and 5 years of age using functional MRI data acquired from 285 children (M/F:137/148).
Using independent component analysis, we identified the spatial maps of 5 networks that are associated with the frontal lobe. Using the AAL template, we then investigated the connection strength to these 5 frontal networks in cerebral regions consisting of the bilateral precentral area, supplementary motor area, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus and in cerebellar regions consisting of the bilateral Lobule III, Lobule IV-V, Lobule VI, Crus I, and Crus II.
We found that the connections between the cerebral regions and the frontal networks peak between 9 and 18 months. Additionally, we discovered that the frontal network exhibits stronger connections with Lobule VI, Crus I, and Crus II, which are believed to be involved in higher

cognitive functions, compared with Lobule III and Lobule IV-V, which are associated with motor functions. This pattern is already evident in the first few months after birth.



Disclosures: **W. Lyu:** None. **K. Thung:** None. **L. Wang:** None. **W. Lin:** None. **S. Ahmad:** None. **P. Yap:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.03/XX39

Topic: I.07. Data Analysis and Statistics

Support: JSPS KAKENHI Grant Number 23K03875
JSPS KAKENHI Grant Number 21K04099

Title: A new fNIRS measurement equipment for improving spatial resolution and removal of systemic components by using near skin blood flow as a reference signal

Authors: *R. TANIGUCHI, T. KOHAMA, H. YOSHIDA;
Grad. school of biology oriented science and technology, Kindai Univ., Wakayama, Japan

Abstract: fMRI is widely used in academic research and clinical settings as a standard method for studying brain function activity. On the other hand, fNIRS has also been increasingly utilized in various fields of brain function measurement in recent years. fNIRS has the advantage of being less restrictive compared to fMRI, allowing for measurements in more natural environments. However, it cannot measure the entire brain like fMRI can. Additionally, there are limitations such as the potential inclusion of scalp blood components.
The holder generally used for fNIRS measurement has transmitting and receiving probes arranged at intervals of 30 mm so that brain activity in the cerebral cortex can be measured. The authors have proposed a new measurement holder and data cleansing method, which has another grid on one axis of the conventional grid arrangement with a 15mm shift, enabling measurement of brain function components at double density, and at the same time measuring skin blood flow at 15mm intervals, which is used as a reference signal. In this study, in order to confirm the effectiveness of this proposed holder, we report the results of a comparative experiment described below with a conventional holder.
In this experiment, we performed finger tapping on subjects whose brain activation area by finger tapping was known in advance. During the finger tapping, we measured the activation area of the motor cortex using both a conventional fNIRS measurement holder and our proposed double density/skin blood flow simultaneous measurement holder. In order to clarify the difference between the two, we first performed a finger tapping experiment by placing the fNIRS measurement holder channel appropriately at a predicted motor cortex activation site. Next, the fNIRS measurement holder was moved 15 mm to the parietal side, and the finger tapping experiment was conducted in the same way as the first experiment.
As a result, in the first experiment, it was possible to identify the activation site of brain activity by finger tapping with both the conventional and the proposed holders. On the other hand, in the second experiment in which the position of the holder was changed, the proposed holder was able to identify the activation site, but the conventional holder with a spatial resolution of 30 mm was unable to confirm the brain activity observed in the first experiment. These results indicate that the proposed holder improves the spatial resolution and makes it easier to identify the

activation sites. In addition, unlike other double-density holders, the proposed holder can be used together with a new data cleansing method that uses skin blood flow near the measurement site as a reference signal.

Disclosures: **R. Taniguchi:** None. **T. Kohama:** None. **H. Yoshida:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.04/XX40

Topic: I.07. Data Analysis and Statistics

Title: A supplemental receiver coil recovers frontal and subcortical fMRI signals under half-volume head coil configuration

Authors: *Y. YUAN, T. TANAKA, D. NISHIYAMA, Y. SHIMADA, I. FUJIMOTO, T. HAJI, A. WADA, M. HARUNO;
NICT CiNet, Osaka, Japan

Abstract: A supplemental receiver coil recovers frontal and subcortical fMRI signals under half-volume head coil configuration
Authors: Yucong Yuan, Toshiko Tanaka, Daisuke Nishiyama, Yasuhiro Shimada, Ichiro Fujimoto, Tomoki Haji, Atsushi Wada, Masahiko Haruno (all NICT CiNet)
Recent advances in virtual reality (VR) technologies have started to impact human emotion and cognition. However, little is known about underlying neural mechanisms. Although fMRI experiments using VR devices are essential, and a VR goggle in front of the eyes is required, it is impossible to locate a standard receiver coil on the front side with the goggle. Absence of the anterior coil leads to a considerable reduction in the signal. In other words, there is the space-signal tradeoff in the VR-fMRI environment. To solve this problem, we tested the co-use of a commercially available elliptical 4-channel receiver coil placed on the participant's forehead with a half-volume posterior head coil to capture brain activity in the frontal and subcortical areas during emotional and cognitive processing. To explore the potential benefits of the frontal 4-channel receiver coil, we first compared the S/N ratio using full (64ch), half-volume (posterior coil part, 40ch) and half-volume + frontal 4ch receiver coils using resting-state fMRI (N=12). We confirmed that adding the frontal 4-channel coil to the back half-volume coil increases the signal-to-noise ratio. Next, we conducted a task-fMRI experiment using an emotional face discrimination task (N=12). This task allowed us to obtain the BOLD signal in the subcortical and prefrontal areas for emotional and cognitive processing. We found that the addition of the frontal 4-channel coil allows us to detect the activity in the amygdala, the striatum, and the ventromedial and lateral prefrontal cortices during the task. These results clarified the benefits of the frontal 4-channel receiver coil to detect BOLD signals in the frontal and subcortical areas, which should be useful in the fMRI experiments of emotion and cognition in VR environments.

Disclosures: **Y. Yuan:** None. **T. Tanaka:** None. **D. Nishiyama:** None. **Y. Shimada:** None. **I. Fujimoto:** None. **T. Haji:** None. **A. Wada:** None. **M. Haruno:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.05/XX41

Topic: I.07. Data Analysis and Statistics

Support: Behavioral and Neural Sciences PhD Program at Rutgers University
US National Science Foundation grant 2219323
National Institute On Aging of the National Institutes of Health under Award Number U01AG052564
McDonnell Center for Systems Neuroscience at Washington University in St. Louis

Title: Regularized partial correlation provides reliable functional connectivity estimates while correcting for widespread confounding

Authors: *K. L. PETERSON[1,2], R. SANCHEZ-ROMERO[1], R. D. MILL[1], M. W. COLE[1]; [1]Ctr. for Mol. and Behavioral Neurosci., [2]Behavioral and Neural Sci. PhD Program, Rutgers Univ., Newark, NJ

Abstract: Functional connectivity (FC) analyses allow us to investigate the brain's communication network, but the quality of inferences depends on the chosen method of FC estimation. One promising method is partial correlation, which can estimate theoretically valid FC from functional magnetic resonance imaging (fMRI) data. Unlike the field-standard FC method of pairwise Pearson correlation, partial correlation considers all measured brain regions when determining the connectivity weights of each pair, allowing it to discard confounded (i.e., false) and indirect connections. However, recent studies have shown partial correlation FC to have extremely poor repeat reliability, which substantially limits its accuracy. We hypothesized that this could be remedied with regularization, which increases estimate stability by reducing overfitting to noise. We therefore tested several established regularized alternatives - graphical lasso, graphical ridge, and principal component regression - against unregularized partial correlation as well as pairwise correlation. They were applied to both empirical fMRI (N=236 participants) and simulated data (N=100 simulations). As expected, all regularized methods substantially improved on the repeat reliability seen with partial correlation, as measured by between-session similarity and intraclass correlation. This stability also increased the accuracy of FC estimates generated by regularized methods, as indicated by their higher similarity to structural connectivity (empirical data) and higher similarity to ground truth networks (simulated data). Graphical lasso achieved especially high accuracy, likely because it better preserved the valid network structure of partial correlation. We then proceeded to test the robustness of the methods to number of timepoints, noise levels, and motion artifacts, with graphical lasso again

performing best. Lastly, we demonstrated the advantage of graphical lasso over pairwise correlation and unregularized partial correlation for two applications of FC: predicting fMRI task activations and predicting individual differences in intelligence and age. Based on these results, we recommend broad use of regularized partial correlation or similar multivariate methods for calculating FC, as they can more validly estimate unconfounded connectivity than field-standard pairwise correlation while overcoming the instability seen in unregularized partial correlation.

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Poster

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Title: Time-domain Signal Alignment Method for Cross-dataset Transfer Learning in Event-Related Potential based Brain-Computer Interface

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Abstract: Recently, more and more electroencephalogram (EEG) datasets have been shared in the Brain-Computer Interface (BCI) field. However, direct use of public datasets for implementing well-working BCI systems is not easy due to the high sensitivity of EEG to equipment and environment [1]. To tackle this issue, we propose a signal alignment (SA) method for transforming an Event-Related Potential (ERP) from one dataset to another. ERPs are slightly different in phase (or time delay), amplitude scale, and direction (positive or negative peak) across datasets due to the differences in the recording environment (paradigm, device, referencing, etc.). Thus, with the basic assumption, we propose a method that makes a linear transform with optimal latency, scale, and reverse factors. Given template ERPs from two different datasets, the latency and reverse factors can be computed using cross-correlation, and the scale factor can be obtained by the ratio of standard deviations of two template ERPs. We evaluated the proposed method with three datasets. First (P3A)[2] and second (P3B) [3] datasets are from the conventional 6 by 6 P300 Speller BCI system where each row/column flashes at a time. The third (P3Face)[4] is also the P300 speller data, but face stimuli were used during

flashing with a random presentation. We attempted to classify targets from non-target epochs with a trained model in two approaches. In the Standard approach, we trained Step-Wise linear discriminant analysis (SWLDA) with one dataset and evaluated it with the other two datasets. But in the proposed approach (SA), signal alignment was conducted before testing a model. The performance was estimated with average precision. As results, standard and SA approaches yielded, for each pair of datasets, 41.9%/46.8% (P3A to P3B), 18.0%/36.5% (P3A to P3Face, $p<0.05$), 31.2%/44.7% (P3B to P3A), 17.4%/35.5% (P3B to P3Face, $p<0.05$), 17.3%/20.2% (P3Face to P3A) and 35.8%/25.6% (P3Face to P3A, $p<0.05$) respectively. These results demonstrate the feasibility of the proposed signal alignment across different datasets and imply that the outcomes may depend on the datasets and type of stimulus.[1] A. Melnik et al., "Systems, subjects, sessions: To what extent do these factors influence EEG data?," Front. Hum. Neurosci., 2017.[2] B. Blankertz et al., "The BCI competition III: validating alternative approaches to actual BCI problems," IEEE Trans. Neural Syst. Rehabil. Eng, 2006.[3] K. Won, et al., "EEG Dataset for RSVP and P300 Speller Brain-Computer Interfaces," Sci. Data, 2022.[4] M. H. Lee et al., "EEG dataset and OpenBMI toolbox for three BCI paradigms: An investigation into BCI illiteracy," Gigascience, 2019.

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Poster

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Title: Reverting the Adverse Effects of White Matter Hyperintensities on Cortical Surface Estimation in Older Population

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Abstract: Introduction:The Human Connectome Project (HCP)-style surface-based brain MRI analysis is a powerful technique that allows precise mapping of the cerebral cortex. However, the strength of the surface-based analysis is yet to be tested in aged people who often show white matter hyperintensities (WMHs) on T2-weighted (T2w) MRI. Here we tested the effects of WMHs on surface-based brain MRI analysis. Methods: We analyzed T1-weighted (T1w) and T2w structural MRI acquired from 43 healthy participants. We removed the effects of subcortical WMHs with two different WMH masks: hand-edited WMH masks and Brain Intensity AbNormality Classification Algorithm (BIANCA)-predicted WMH masks. To evaluate the quality of surface-based analysis, we used stereological quality control (QC) by two blinded radiologists and automated surface QC based on an HCP-YA database. We compared the QC scores across the default pipeline and customized pipelines with hand-edited WMH masks and BIANCA-predicted WMH masks. Results: We found substantial surface estimation errors in the default pipeline in which WMHs were mislabeled as part of the GM due to the relatively low and high intensities of WMHs in T1w and T2w MRIs, respectively. The proposed pipeline improved the quality of surface estimation. Two blinded raters indicated a reduction of the surface estimation errors in the proposed pipeline. The surface QC metric supported better surface analysis quality of the proposed pipeline with the reduction of outliers in the surface metrics. Discussion: We show that WMHs may result in surface estimation errors, yielding erroneous values in the surface metrics such as cortical thickness and myelin maps. Because WMHs are common in the aged population, we recommend intensive QC in the surface analysis of MRI data in the aged population. The incorporation of WMH masks is expected to improve the quality of surface based analysis.

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Poster

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Title: YAEL: Yet Another Electrode Localizer for iEEG

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Abstract: Intracranial electroencephalography (iEEG) provides a unique opportunity to measure human brain function with implanted electrodes. We describe the YAEL (Yet Another Electrode Localization) software package for accurately determining electrode locations, a key step in neuroscience inference.
Existing workflows require manually selecting each electrode from the patient's computed tomography (CT) scan, a time consuming and error-prone process. YAEL expedites this process with automated electrode localization. In modern clinical practice, iEEG patients are implanted with stereotactic (sEEG) electrode shafts, each containing many contacts. YAEL users may click on only two contacts on a given shaft and YAEL will automatically select all remaining contacts, accounting for any bends in the shaft introduced during the surgical insertion process.
After identifying the approximate location of each electrode, YAEL applies a refinement process. Electrode locations are automatically adjusted using nearby CT densities. While some workflows downsample the CT to match the resolution of the pre-surgical MRI, YAEL uses the original CT for more accurate localization. This is important for identifying the location of the electrode relative to cortical lamina or small subcortical structures.
A common source of error is the confusion of contacts on nearby sEEG shafts. To ensure that electrodes are mapped correctly, YAEL provides simultaneous viewing of 3D cortical surface models and 2D MRI slices, together with all electrode positions. Both penetrating sEEG electrodes and grids and strips of surface electrocorticographic (ECoG) electrodes are supported, along with the brain shift compensation sometimes required for accurate ECoG localization. Viewer parameters, such as CT threshold, can be adjusted on-the-fly for quick troubleshooting. YAEL's integrated graphical-user-interface (GUI) is designed to be flexible and easy to use. Installing YAEL automatically installs Advanced Normalization Tools (ANTs) and NiftyReg for CT-MRI co-registration (FSL-FLIRT is also supported). Users may export the completed table to comma-separated value (CSV) files that contains electrode locations in three coordinate systems; four anatomical labels estimated from different anatomical segmentations and parcellations; and MNI template coordinates for group analyses. YAEL is fully integrated with the RAVE iEEG analysis suite and is freely available at https://rave.wiki .

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Poster

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Title: Identifying and combining homogenous signals for better brain parcellation in functional neuroimaging analysis

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Abstract: Many analyses of fMRI data rely on clustering multiple voxels into discrete regions and producing representative mean time series. Hierarchical agglomeration techniques, such as the Ward method, combine voxels into clusters by optimizing a similarity metric between potential merges. There are two potential issues with this approach. First, the standard approach merges clusters based on a Euclidean distance metric, which assumes that signals are similar in magnitude, rather than simply exhibit correlated activity patterns. Secondly, without a principled stopping point, clusters may be over-combined, such that anti-correlated signals are averaged together. Here, we assess the relative performance of Euclidean distance compared to homogeneity (mean correlation) as a similarity metric, and develop a method for determining the best number of clusters in the parcellation. We collected resting state fMRI data from 29 subjects. Following standard preprocessing, we compared cluster construction using the Ward agglomeration method to two custom variants of hierarchical clustering. In the first variant, Euclidean distance was the metric for assessing potential cluster mergers, as in the standard Ward method, however, the distance was divided by the correlation of averaged signals (or homogeneity) between the proposed clusters. Zero and negative homogeneity values were reassigned to a tiny value. This modification dramatically increases the distance metric of poorly correlated cluster distances, creating a clear stopping criterion based on a standard elbow approach. A second variant replaces the Euclidean metric with correlation distance, which, as stated above, no longer requires clusters to have similar magnitudes to combine. To ensure the merged features are on equal footing, the time series are Z-scored before clustering.To assess how these variants affected the clusters we examined N=200 clusters produced for each method. The correlation distance variant increased the mean cluster size, by producing fewer small clusters, and reduced the cluster size variability compared to the original Ward method or the homogeneity-scaled Euclidean variant. We will present examples from these solutions and a comparison of differential outcomes for a functional connectivity based analysis using each of these methods. Our method of defining and aggregating neuroimaging signals improves on current practices by producing more homogenous solutions and implementing a data-driven stopping mechanism. These changes are not trivial, as many neuroimaging projects investigating a diverse range of topics are reliant on accurate signal aggregation.

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Poster

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Topic: I.07. Data Analysis and Statistics

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Title: Deep learning-based feature extraction from intracranial electroencephalography recorded from epilepsy patients

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Abstract: Background
Although advancements in deep learning (DL) techniques have identified which parts of an image are essential for classification, revealing electrophysiological signal features extracted by DL remains a difficult task. Signal classification has been reported to help doctors diagnose disease and determine the treatment approach for epilepsy patients. However, due to lacking of methods that understandably disclose the detected feature by DL model, those classification studies rarely lead to improved comprehension of epilepsy electrophysiology. To address this problem, we developed a new method to clarify a feature DL model learned from intracranial electroencephalogram (IEEG) signals from epilepsy patients. The revealed feature was evaluated by comparing it with other conventional signal features.
Methods
IEEG signals recorded from 21 refractory epilepsy patients with multiple etiologies (including 109 seizures) were analyzed retrospectively. The early phase signals of epileptic seizures (EPES) (0 to 10 seconds after onset) and interictal states were classified by two models, and their classification accuracies were compared: a one-dimensional convolutional neural network model named Epi-Net and a support vector machine (SVM) model using a spectral power of 8 frequency bands (δ, θ, α, β, low, high-γ, HFO, and 250–500 Hz) and phase amplitude coupling between the γ amplitude and the α and β phases. Then, a modified integrated gradients (mIG) method was applied to Epi-Net to reveal the relative contribution of each frequency amplitude to characterizing EPES. Next, we defined the product of powers multiplied by the contribution as a data-driven epileptogenicity index (d-EI). By comparing the d-EI with other features, its accuracy in detecting EPES was assessed. Finally, we compared the d-EI among the electrodes to estimate how it affects seizure onset zone identification.
Results
Epi-Net outperformed the SVM, with an AUC of 0.944 ± 0.067, which was significantly larger than that of the SVM (0.808 ± 0.253; p = 0.025). The mIG disclosed that Epi-Net focused on increased powers of 17–92 Hz and >180 Hz when classifying IEEG signals of EPES. Seizure detection accuracy of d-EI was the highest among all features. Moreover, the surgical resection of areas showing a larger increase in d-EI was significantly associated with seizure outcomes.
Discussions
D-EI, a new IEEG feature learned by Epi-Net, was extracted with mIG. Identifying the pattern of contribution of each frequency component to detecting epileptic seizures is expected to lead to an enhanced understanding of epilepsy electrophysiology.

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Poster

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Title: Toward a deep neural network simulator of brain activity on fast time scales: Correspondence between EEG and Transformer-based model responses to naturalistic audio stimuli

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Abstract: A functional correspondence between the brain and deep neural networks (DNNs) may allow DNNs to be used as simulators of the brain, which can be used to evaluate the effects of specific sensory and physiological stimuli on the brain. This could lead to the development of novel interventions based on DNN models for the treatment and enhancement of cognitive abilities. Brain oscillation ranging from a few to over 100 Hz is involved in various healthy and pathological brain functions. Indeed, methods have been developed to intervene in such oscillatory activity using external stimulation. Therefore, interventions where DNNs are used as brain simulators also need to handle such fast activity. However, fMRI cannot capture this. In addition, most of the existing studies on the correspondence between the auditory brain and DNNs have focused only on speech. Therefore, the correspondence of their responses to more general auditory stimuli is still unknown.
Here, therefore, we used electroencephalography (EEG) to measure fast brain activity from native Japanese speakers listening to a variety of naturalistic auditory stimuli. During the EEG recording, they were exposed to documentary videos containing Spanish or Russian narration and environmental sounds, as well as short video clips to which various sound materials used in TV programs were randomly attached. The power spectral density of the obtained brain responses was predicted by linear regression from the responses of the self-supervised audio spectrogram Transformer. This is a DNN model that takes a mel spectrogram as input and is pretrained on various sound data in a self-supervised learning framework.
The results showed that, as a whole, the predictions were accurate to a certain degree for both the data from the experiments with documentary and short video clip stimuli. In addition, the data from the short video clip experiment showed a dependence of prediction accuracy on electrode position. Specifically, prediction accuracy was lower for the posterior electrodes. This is reasonable because the occipital lobe is mainly responsible for visual processing, and auditory stimuli are difficult to access there. On the other hand, no such dependence was observed in the data from the documentary video experiment. This may be due to the fact that in the short clips, there is no relationship between video and sound, whereas, in the documentary video, they are originally associated. In both conditions, there was no dependence on the frequency band of the

EEG.
The present results provide insights into the brain regions and frequency ranges in which it is appropriate to model brain activity responses to auditory stimuli in DNNs.

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Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

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Title: Densenet and support vector machine classification of major depressive disorder with vertex-wise cortical features

Authors: V. BELOV[1], A. ALEMAN[2], Z. BASGOZE[3], F. BENEDETTI[4], A. GONUL[5], I. H. GOTLIB[6], H. J. GRABE[7], N. GROENEWOLD[8], T. HAHN[9], L. K. M. HAN[10], T. C. HO[11], T. KIRCHER[12], M. LI[13], D. M. A. MEHLER[14], E. POZZI[10], J. RADUA[15], M. D. SACCHET[16], J. C. SOARES[17], D. STEIN[8], S. THOMOPOULOS[18], Y. J. TOENDERS[10], Y. VIVES-GILABERT[19], M. WALTER[13], K. WITTFELD[20], C. A. ZARATE, JR[21], D. VELTMAN[22], C. R. K. CHING[18], L. SCHMAAL[10], P. M. THOMPSON[18], ***R. GOYA-MALDONADO**[1];
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Angeles, CA; [12]Philipps Univ. Marburg, Marburg, Germany; [13]Unversitätsklinikum Jena, Jena, Germany; [14]Univ. of Aachen, Aachen, Germany; [15]Inst. d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [16]Harvard Med. Sch., Boston, MA; [17]The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [18]USC, Los Angeles, CA; [19]Univ. de València, València, Spain; [20]Univ. of Greifswald, Greifswald, Germany; [21]Natl. Inst. of Mental Hlth., Bethesda, MD; [22]Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: The complex and heterogeneous nature of major depressive disorder (MDD) has sparked ongoing debates regarding the association between morphological brain alterations and the clinical manifestation of the disorder. Previous attempts to differentiate MDD patients from healthy controls (HC) using linear machine learning approaches based on segmented cortical features have yielded low accuracies. However, deep learning techniques applied to more refined neuroimaging data show promise in identifying diagnostic and predictive biomarkers for MDD by capturing intricate non-linear patterns. In this study, we leveraged a globally representative dataset from the ENIGMA-MDD working group, comprising individuals with MDD (N=2,772) and HC (N=4,240), which allowed for a robust analysis with generalizable outcomes. Our objective was to assess the classification performance of two methods: DenseNet and Support Vector Machine (SVM). We hypothesized that integrating vertex-wise cortical features - thickness, curvature, and sulcal depth - would increase classification accuracy compared to individual features, and that DenseNet would outperform SVM. To mitigate potential confounding effects across multiple sites, we utilized the ComBat harmonization tool. Both classifiers demonstrated performance close to chance when evaluated on unseen sites (DenseNet: 51% balanced accuracy; SVM: 53% balanced accuracy). Slightly improved classification accuracy was achieved when cross-validation folds included participants from all sites (DenseNet: 58% balanced accuracy; SVM: 55% balanced accuracy), indicating the influence of site-related factors. Overall, the integration of vertex-wise morphometric features and the utilization of non-linear classifiers did not facilitate clear differentiation between MDD and HC. These findings underscore the current limitations in utilizing these techniques in this particular combination of vertex-wise brain features for the classification of MDD. Future research will explore more sophisticated approaches to integrating information from other MRI modalities, such as functional MRI and diffusion MRI, in an attempt to increase the accuracy of diagnostic tasks related to MDD.

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Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

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Title: Improving MEG Inverse Model Identification for Brain Cortical Connectivity Analysis

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Abstract: State-space models find extensive applications across various scientific domains, including econometrics, controls, and neuroscience. In computational neuroscience, they play a crucial role in solving the neuromagnetic inverse problem by estimating latent activity from out-of-scalp recordings. While sparsity-aware state estimation techniques have significantly enhanced source localization accuracy, precise identification of state-space model parameters remains a challenging task. Current solutions, such as the Expectation-Maximization (EM) algorithm and its variants, face difficulties due to non-convex optimization and slow convergence. Reliable model identification is essential for studying network-level properties of cortical activity. In this work, we present an improved sparsity-aware EM-based source localization technique that surpasses existing methods. We introduce adaptive sparse state-space modeling, which incorporates a data-driven adaptation method to enhance convergence rate, thereby making it more applicable in real-world scenarios. We showcase the efficacy of our proposed methodology through realistic simulation studies, focusing on the magnetoencephalography (MEG) inverse problem as a use case. Our results demonstrate the substantial improvements offered by the proposed method, consolidating its superiority in neuroscience applications. In addition, we apply our method to a set of experimentally recorded MEG data from stroke patients undergoing clinical rehabilitation and successfully demonstrate the network-level changes correlated to their cognitive improvements across recovery checkpoints.

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Poster

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Topic: I.07. Data Analysis and Statistics

Title: When brain-phenotype associations are studied, it is crucial to know the intraclass correlations of the measured variables

Authors: *M. K. BASINSKA;
Med. Univ. of Gdansk, Gdansk, Poland

Abstract: Linking behavioral phenotypes to brain structure and function is a persistent challenge in mental health research. Some phenotypes, like cognitive ability, are known to be relatively stable over time, while others, like suicidality, are much less stable. Mental health phenotypes are often measured with assessment scales and questionnaires that aim to target inter-individual differences, with the assumption that the phenotype is relatively stable over time. I used a computer simulation to find to what extent the use of questionnaire data can hinder attempts to establish reproducible brain-phenotype associations by reducing test power. In the simulation, I considered predictors (independent variables, IV) and phenotypes (dependent variables, DV) with intraclass correlations (ICC) equal to 0.3 and 0.6 (as calculated over measurements separated by days rather than minutes or seconds). Inter and intra-individual variance of the IV contributed to the same extent to the inter and intra-individual variance of the DV in a linear fashion (r = 0.1, 0.2, and 0.5). Samples of 50, 100, 200, 500, and 1000 individuals were simulated, with 10 time points for each individual. Each combination of parameters was simulated 1000 times. The average level of the DV (ADV) over all time points was calculated for each individual. Since averaging over multiple time points cancels out intra-individual variance, ADV was considered a proxy of questionnaire measurement. I considered the correlation of not averaged IV and DV at one time point a reference to compare the correlations of the ADV with one measurement or the average of 2, 5, and 10 measurements of the IV. For a pair with ICCs = 0.3, the correlation of one measurement of IV with ADV underestimated the true correlation by 37.7-41.5% of the reference effect (for ICC = 0.6 by 17,6%-21,3%). As a consequence, power was reduced by up to 41 p.p. For ICC = 0.3 using 10 averaged measurements of the IV as a predictor made the effects well estimated. For ICC = 0.6 and 5 averaged measurements, there was nearly no underestimation. The above results show that for variables with low ICCs, when DV is measured with a questionnaire and IV with a direct behavioral or neuroimaging measure, some variance is left unexplained. The results also suggest that this challenge can be addressed by the use of longitudinal designs along with direct behavioral measures of phenotypes. It is not obvious how the results will generalize to multivariable models, but it seems unlikely that the consequences of averaging of the DV may disappear entirely. This issue may be explored in further work, along with different combinations of IVs' and DVs' ICC and varying timescales.

Disclosures: M.K. Basinska: None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.15/XX50

Topic: I.07. Data Analysis and Statistics

Title: Unveiling the neural symphony: EEG-based song classification and enjoyment assessment

Authors: *I. AGARWAL[1], P. PANDEY[2,3];
[1]Biol. Sci., Indian Inst. of Sci. Educ. and Research, Mohali (IISER Mohali), Mohali, India; [2]Univ. of Rhode Island, South Kingstown, RI; [3]Computer Sci. and Engin., Indian Inst. of Technol. (IIT) Gandhinagar, Gandhinagar, India

Abstract: Music has a profound impact on the human brain, influencing emotions and eliciting diverse responses. Understanding the neural correlates of music perception and enjoyment can have far-reaching implications in fields such as music therapy, personalized music recommendations, brain-computer interfaces (BCI), etc. In this study, we investigate the feasibility of classifying songs and assessing their enjoyment levels using electroencephalogram (EEG) data collected during music listening sessions. To conduct our research, we leverage the publicly available Naturalistic Music EEG Dataset—Tempo (NMED-T) obtained from the Stanford Digital Repository. This dataset consists of EEG recordings, familiarity ratings, and liking scores provided by 20 subjects aged 18-29 years, with a mean age of 23 years and six female participants. All participants reported normal hearing, fluency in English, and no cognitive or decisional impairments. Moreover, 17 of the participants had received music training for an average duration of 8.4 years. On average, participants reported listening to music for 14.5 hours per week. The analysis of the EEG data involves several steps. Initially, we apply a cross-frequency coupling (CFC) method called phase-amplitude coupling (PAC) to examine the inter-sensor brain dynamics across seven brain rhythms. PAC provides valuable insights into the coordination and communication between different frequency bands within the brain. Next, we utilized dynamic graph centrality, specifically focusing on broadcast and receive measures, to investigate the connectivity patterns among brain regions. By analyzing how information propagates and is received within the brain network, we can better understand the underlying neural mechanisms associated with music perception and enjoyment. We utilized feature selection techniques to extract relevant features from EEG data, specifically focusing on gamma rhythm data and identifying features with positive relief scores. We utilized Support Vector Machine (SVM) for training the model on the selected features, and developed a binary classification framework designed to identify the songs being played based exclusively on EEG data. Additionally, we employ SVM classification to predict the liking scores of the songs. Together, this study sheds light on the intricate relationship between music enjoyment and brain activity. Overall, our investigation demonstrates the potential of EEG-based song classification and enjoyment assessment in various domains, ranging from clinical applications to music recommendation systems.

Disclosures: **I. Agarwal:** None. **P. Pandey:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

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Osher Center for Integrative Medicine

Title: Preserving gastric peristalsis during motion correction for abdominal cine-MRI data - A low-rank tensor-based approach

Authors: *R. SCLOCCO[1], J. COLL-FONT[2], C. NGUYEN[2], B. KUO[2], V. NAPADOW[1]; [1]Spaulding Rehabilitation, Harvard Med. Sch., Boston, MA; [2]Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA

Abstract: Evaluation of gastric function is important for the clinical diagnosis of multiple disorders. Recently, magnetic resonance imaging (MRI) applications to the study of gastric function in humans have started to incorporate dynamic volumetric imaging. These approaches allow for continuous 3D coverage of the gastric region without requiring breath holding, hence providing measurements of gastric emptying and motility with a single, non-invasive test. However, motion artifacts (e.g., respiration) require techniques to mitigate inter-frame misalignments. Most standard off-line motion compensation methods use a fixed motion-free template as reference to register the motion-corrupted images. However, while this approach can mitigate undesired sources of motion, it can also impact gastric peristaltic estimates. We propose to overcome this limitation by generating a respiration-free template of the original images that eliminates respiratory motion, while preserving gut dynamics. Our Gastric Low-Rank Tensor-based approach uses a low-rank tensor (LRT) model to separate the temporal components that correspond to breathing motion from those related to gut motion. The key assumption of the approach is that the two main sources of motion (i.e. respiration and peristalsis) are uncorrelated and, hence, appear as orthogonal components of the LRT decomposition. The algorithm includes three main steps, namely (i) LRT decomposition, (ii) separation of the respiratory and gut motion components, and (iii) registration to the respiratory-free template. We perform subject-specific separation between peristaltic and respiratory motion by taking advantage of the spatially localized nature of the peristaltic motion - i.e. respiratory motion affects the entire abdomen,

while peristaltic motion is concentrated on the stomach. As a proof of concept, we applied the algorithm on gastric cine-MRI data in fasted and fed state. Images were collected on a 3T scanner using a real-time 3D cine sequence not requiring breath holding (2.4 s/volume, 72 abdominal coronal slices, 125 volumes), preceding and following the ingestion of a contrast meal. Application of the proposed algorithm showed successful recovery of clean gastric peristalsis both in the fed and fasted state, as demonstrated by the data profile showing oscillations at 3cpm, and by the reduced fluctuations in the position of the gastric center of mass over time. Our motion correction approach effectively removes respiratory noise from abdominal cine-MRI data while preserving gastric peristalsis, thus providing a useful pre-processing tool for the non-invasive evaluation of gastric functional impairments.

Disclosures: R. Sclocco: None. **J. Coll-Font:** None. **C. Nguyen:** None. **B. Kuo:** None. **V. Napadow:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

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Program #/Poster #: PSTR311.17/XX52

Topic: I.07. Data Analysis and Statistics

Support: Innovatice Science and Technology Initiative for Security Grant Number JPJ004596

Title: A denoising filter for the simultaneously recorded EEG-fMRI data by using an autoregressive model with exogenous input with carbon-wire loop signals

Authors: *T. OGAWA[1], T. KURODA[1], R. KOBLER[1,2], M. TSUTSUMI[1], T. KISHI[1], M. KAWANABE[1,2];
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Abstract: Artifact removals for electroencephalography (EEG) data measured in the magnetic resonance imaging (MRI) scanner have been developed to extract and study brain dynamics. In highly magnetic fields, EEG sensors capture not only brain activity but also artifacts of mechanical (gradient, vibration of the helium pump) and physiological (ballistocardiogram: BCG, head movements) origin. Carbon-wire loops (CWLs) placed on the EEG cap capture a majority of these artifacts independently from brain activity, thereby being suitable for reducing the artifacts with an adaptive regression technique (van der Meer et al., Neuroimage, 2016). Nonetheless, this technique has been limited to recording EEG and CWL signals simultaneously. Here, we propose a machine learning technique to predict CWL-denoised EEG signals. In particular, we use noisy EEG as input and the target as the CWL-denoised EEG. The noise reduction model consists of autoregressive models with exogenous input (ARX) to fit the training EEG data. We primarily examined 63-ch EEG data recorded from a phantom as a baseline and also applied the method to 63-ch EEG datasets from four subjects. To estimate the

model's generalization capabilities, we considered within-subject and day, within-subject across days, and subjects' train/test split scenarios. We found that the trained model could accurately predict time courses of CWL-denoised EEG signals from the noisy EEG on held-out test data. Additionally, we confirmed that the residuals were sufficiently whitened with a Kolmogorov-Smirnoff test. Altogether, our preliminary findings suggest that our approach has the potential to improve EEG data denoising for legacy EEG-fMRI datasets that were recorded without CWLs.

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Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.18/XX53

Topic: I.07. Data Analysis and Statistics

Title: A showcase of faults in gradient-based deep learning explanations for Neuroimaging

Authors: *N. LEWIS[1], A. FAGHIRI[2], V. CALHOUN[3];
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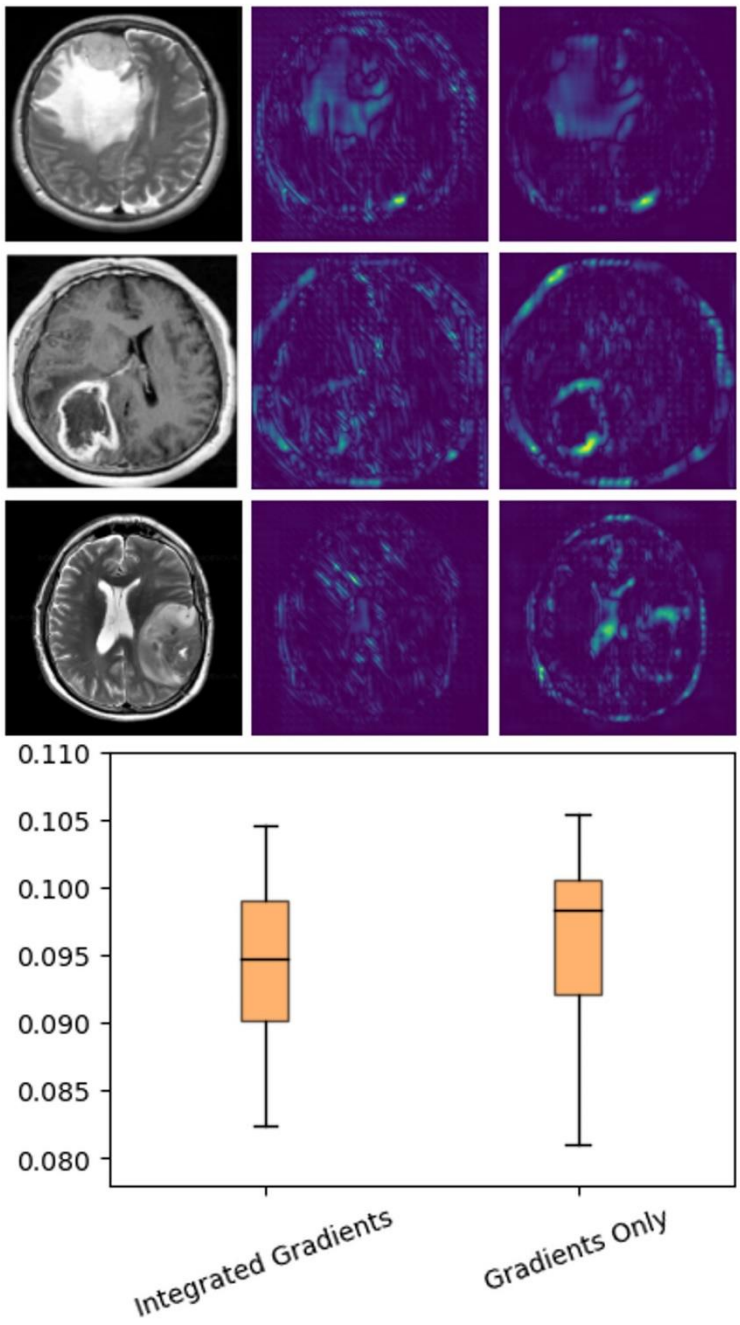
Abstract: Explainable AI in the medical field has exploded in the last few years. However, recent work in the broader field of explainability has revealed extensive problems with various XAI methods, particularly post-hoc gradient-based methods. First and foremost, gradient-based saliency methods have been found to be unreliable, unable to capture all correlations learned by the model, and generally problematic. In this paper, we will elucidate some of these issues that are particular to the medical field.
We will show some of these problems by experimenting with a single dataset of sMRI data containing controls and patients with brain tumors. We train a state-of-the-art resnet model to classify the patients vs. controls and then compute the gradients-only saliency and integrated gradients (IG), and compare these relevancy maps with a ground truth representation of the patients with brain tumors. The ground truth representation is a mask that covers only the tumor location. Beyond the ground truth estimation, we will also test the maps' stability over differently seeded models to investigate a phenomenon known as underspecification. This is a phenomenon in which two models can be equally optimal, but also be entirely different functions with different weight values. This phenomenon can impact both performance on holdout data and any explanation associated with the model. In order to showcase this effect, we used the same dataset for 20 separate models and tested how similar the saliency maps were over all 20 models.
Our results show, even with a generally accurate model, the saliency maps capture only a small percentage of the truly relevant information. Additionally, we found that the maps themselves vary wildly over the 20 models. Overall, this poster presents some of the drawbacks behind gradient-based explanatory methods and showcases some of the pitfalls, in the hopes of generating discussion on how best to improve these explanatory methods.



Top: 3 examples of subject MRI scans with tumors (left) along with the corresponding IG maps (middle) and grads-only maps (right).
Bottom: the percentage of the IG (left) and grads-only (right) maps that overlap with the ground truth regions, the tumors themselves.

Disclosures: **N. Lewis:** None. **A. Faghiri:** None. **V. Calhoun:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

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Program #/Poster #: PSTR311.19/XX54

Topic: I.07. Data Analysis and Statistics

Support: NIH R01 MH129395
NIH F32 MH125540

Title: Strategies for Motion- and Breathing-Robust Estimation of fMRI Intrinsic Neural Timescales

Authors: *A. GOLDBERG[1], J. D. POWER[2], G. HORGA[1,3], K. WENGLER[1,3];
[1]New York State Psychiatric Inst., New York, NY; [2]Weill Cornell Med., New York, NY;
[3]Psychiatry, Columbia Univ. Med. Ctr., New York, NY

Abstract: Intrinsic neural timescale (INT) is a resting-state fMRI (rs-fMRI) measure reflective of the time window of neural integration within a brain region with relevance to neuropsychiatric disorders. Despite its relevance, physiological artifacts, which can impinge on the validity of fMRI findings, have not been systematically considered in INT estimation. Two such artifacts, head motion and respiration, pose serious issues in rs-fMRI studies. Here, we analyzed how two preprocessing strategies targeting these artifacts—frame censoring and global signal regression (GSR)—affect INT estimation. We used a subset of the HCP Young Adult dataset with runs annotated for breathing patterns (Lynch et al., 2020) and at least one "clean" run that was free from breathing artifacts and head motion (frame displacement<0.2 mm for >1000/1200 frames). The subset of analyzed data comprised these "clean" runs and other "non-clean" runs from the same participants (n = 46). All data were preprocessed using the HCP minimal preprocessing pipeline and nuisance regression was performed with the average WM and CSF signal, plus 6 motion parameters and their 1st derivatives. For non-clean runs, nuisance regression also included: 1) both frame censoring and GSR; 2) only frame censoring; 3) only GSR; or 4) neither. INT maps were calculated from autocorrelation functions (ACF) estimated in three ways: 1) a standard approach using the full timeseries after despiking frame censoring (when applied) (Wengler et al., 2020); 2) using blocks of contiguous frames after frame-removal censoring (when applied) (Raut et al., 2020); or 3) using Lomb-Scargle periodograms (VanderPlas, 2018) after frame-removal censoring (when applied). We evaluated the ability of frame censoring and GSR to correct for artifacts by comparing the non-clean runs to their respective clean run within a subject. We found that using both frame censoring and GSR yielded the lowest INT estimation error. We also found that GSR significantly improved INT estimation for runs with deep breaths ($t=-2.5$, $p=0.021$). Randomly applying frame censoring to the clean runs revealed for all three ACF-estimation methods that frame censoring itself biased INT values regardless of motion (more censored frames caused more INT underestimation; $t=-14.3$, $p<0.001$), with the standard approach being least susceptible to this bias. Importantly, bias correction is possible through regression-based adjustments for subject-level frame censoring. Overall, these results simultaneously reflect the utility of frame censoring and GSR in minimizing physiological artifacts, as well as the importance of accounting for potential confounds in INT estimation.

Disclosures: **A. Goldberg:** None. **J.D. Power:** None. **G. Horga:** None. **K. Wengler:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

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Topic: I.07. Data Analysis and Statistics

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Brain and Behavior Research Foundation's NARSAD Young Investigator Award
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Title: Innovative imaging techniques in the study of balance and the brain in autistic youth

Authors: ***A. R. BLOCK**[1], O. SURGENT[3], B. TRAVERS[3], J. GUERRERO-GONZALEZ[4], N. ADLURU[2], D. DEAN, III[4], A. L. ALEXANDER[4], G. R. KIRK[4], S. KECSKEMETI[4]; [1]Kinesiology, UW-Madison, Madison, WI; [2]UW-Madison, Verona, WI; [3]Univ. of Wisconsin-Madison, Madison, WI; [4]Waisman Ctr., Madison, WI

Abstract: Motor challenges, including decreased postural control and balance ability, are prevalent features of autism spectrum disorder (Harris, 2017; Travers et al., 2013), and yet, the neurobiological mechanisms driving these challenges remain largely unknown. Evidence suggests that the brainstem may strongly contribute to autism features and motor behavior (Dadalko & Travers, 2018; Rimland et al., 1964), making it a key area for further investigation. Despite this evidence, the low resolution of traditional brain imaging techniques makes it difficult to image the brainstem *in vivo*. Previous voxel-based analyses revealed autism-specific changes in the brainstem as a result of a balance intervention (Surgent et al., 2021); however, the study's use of conventional brain imaging methods limited its ability to capture the anatomical complexities of the brainstem. This study employs a novel post-processing method for brain imaging (TiDi-Fused processing) to enhance quantification of brainstem structures (Guerrero-Gonzalez et al., 2021) with the purpose of investigating if neuroplasticity in the brainstem is related to balance improvement in autistic individuals. We utilized data from a randomized control trial (#NCT02358317) involving balance intervention and brain imaging in autistic and non-autistic adolescents. Outcome variables included balance improvement and corresponding brain plasticity as a result of balance intervention. The TiDi-fused method proved to be an effective form of post processing brain images, decreasing the coefficient of variance by an average of 3.7%, in addition to demonstrating sharper gray-white matter boundaries and improved apparent resolution. Further, we were able to replicate previous voxel-based analysis findings, showing autism specific brainstem changes in FA ($t(11) = 1.915$, $p = 0.0819$) and ICVF

($t(11) = -1.958$, $p = 0.0761$) in the brainstem, and, with the TiDi-fused method, we were able to confirm that these changes were located in the left SCP. Together, these results suggest not only that the TiDi-fused method is an accurate and reliable post processing technique for enhancing visualization and quantification of brainstem structures in traditionally acquired DWI datasets, but also that neuroplasticity in the SCP plays an important role in balance for autistic individuals in a way that is distinct from their non-autistic counterparts.

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Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

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Program #/Poster #: PSTR311.21/XX56

Topic: I.07. Data Analysis and Statistics

Support: NSF GRFP Grant DGE-2146755

Title: Modeling neural features predictive of cognitive performance with a gamma generalized linear model

Authors: *M. HEDLUND, B. REID, J. PARVIZI, T. COLEMAN, V. BUCH;
Stanford Univ., Palo Alto, CA

Abstract: Identifying neural features that modulate cognitive performance is a core question in cognitive neuroscience. Intracranial electroencephalography (iEEG) provides unique and unparalleled insights into rapid human brain state dynamics. We aimed to study the predictive effect of subsecond spontaneous neural features on upcoming single-trial reaction times (RT). We collected data from 13 adult human subjects undergoing iEEG monitoring for epilepsy as they answered basic true/false math questions. RT was used as a measure of cognitive performance. Spectral power and phase-locking value-derived communicability, which is a graph theoretic measure of network-wide information flow in and out of each node, were calculated in four canonical frequency bands for every electrode. Features that have a statistically significant relationship with RT were found using a univariate gamma GLM and comparison linear regression model. To assess goodness of fit for each distribution, we calculated the empirical and theoretical cumulative distribution functions and compared the Kolmogorov-Smirnov (KS) statistics. We showed that the conditional distribution of the RT given neural features is better modeled using a generalized linear model (GLM) with a gamma distribution and log link function than with linear regression, which assumes a Gaussian distribution. The mean KS statistic was .349 (.069 SD) for the Gaussian distribution and .241 (.130 SD) for the gamma

distribution. On average, the gamma KS statistic was lower than the Gaussian by .107 (.150 SD), indicating that the gamma distribution was a better fit for the data. Using the significant features as regressors, a multivariate gamma GLM was trained with an 80/20 train/test split and 5-fold cross-validation. The number of features used as regressors were varied in order to find the optimal prediction error, selecting the features with the highest weights as the number of features. The average standard prediction error is 1.36s (.352 SD). Without knowledge about the neural features, the best prediction for the RT is the sample mean. In all subjects, conditioning on the neural data reduced the standard prediction error, with a mean improvement of 19.32% (7.48 SD). Therefore, conditioning on the neural features exhibits higher predictive power than the marginal distribution of RTs. We conclude that spontaneous neural features, prior to trial onset, can predict upcoming RT using a gamma GLM. This modeling approach may be used in the future to create a closed-loop cognitive neural state decoder and empower therapeutic strategies for cognitive disability.

Disclosures: **M. Hedlund:** None. **B. Reid:** None. **J. Parvizi:** None. **T. Coleman:** None. **V. Buch:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

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Program #/Poster #: PSTR311.22/XX57

Topic: I.07. Data Analysis and Statistics

Support: NSF Grant 1942712

Title: Leveraging EEG Signals and Motion Artifacts for Accurate Gait Event Prediction: A Machine Learning Approach

Authors: *R. KANKAR[1,2], H. HUANG[1];
[1]Univ. of Central Florida, Orlando, FL; [2]Univ. of Central Florida, Orando, FL

Abstract: EEG, a primary mobile brain imaging technique, often contends with motion artifacts—large electrical signals generated by movement, which mask underlying brain activity. Traditionally, these are removed using signal processing methods. Our lab uses a dual-layer EEG system to record standard scalp electrical activity and isolated motion artifacts, providing an expanded toolset for signal processing. This dual-layer system includes an inner layer to measure electrical activity from scalp-interfacing electrodes (like standard EEG), and an outer layer to measure activity from outward-facing electrodes in contact with a conductive fabric cap—presumably mainly noise and motion artifacts.The purpose of this study was to determine whether gait events could be accurately predicted using machine learning techniques. Our dataset is from mobile brain imaging study in the lab that recorded dual-layer EEG as human participants (n=14) responded to small discrete surface treadmill belt perturbations while walking. The belt perturbations were brief increases and decreases in treadmill belt speed at

either left heel strike or left mid-stance. The experimental protocol included periods of unperturbed (normal) and perturbed walking. The dataset used here includes both perturbed and unperturbed walking conditions from 14 subjects. The perturbed dataset represents instances of unexpected obstacles during walking, while the unperturbed dataset captures regular, unobstructed walking. We were interested in predicting typical gait events, the left and right heel strikes and toe offs..Machine learning models—Random Forest, Logistic Regression, and SVMs—were trained using the motion artifact layer alone, the full inner layer (both good and bad channels), and only the good inner layer channels. Models trained on the outer/motion artifact layer showed the highest performance, highlighting the artifacts' value in gait event prediction. Models trained on both good and bad inner layer channels outperformed those trained only on good channels, indicating even perceived EEG noise can have gait prediction value.Further evaluation of advanced neural networks showed LSTM-equipped RNNs effectively utilized the temporal dependencies in EEG and motion artifact data, significantly boosting prediction accuracy.This study revolutionizes our understanding of brain dynamics and walking biomechanics, suggesting EEG, when fully leveraged, can offer insights beyond traditional brain dynamics assessments. This could facilitate research into age and disease-related mobility and cognitive impairments, broadening neuromechanics research's future scope.

Disclosures: **R. Kankar:** None. **H. Huang:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.23/XX58

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant U01NS117839

Title: Surgical and Neurophysiological Analytic Methods for Human Single-Neuron Recordings with DIXI Medical Microdeep Micro-Macro Depth Electrodes

Authors: *M. L. DARWIN[1], J. ZHENG[2], U. RUTISHAUSER[3], S. OJEMANN[4], D. R. KRAMER[4], J. A. THOMPSON[4];
[1]Neurosurg., CU Anschutz Med. Campus, Aurora, CO; [2]Boston Children's Hosp., Boston, MA; [3]Neurosurg., Cedars Sinai Med. Hosp., Los Angeles, CA; [4]Neurosurg., Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Single neuron recordings offer unparalleled temporal and spatial resolution to advance the field of cognitive neurophysiology as never before afforded. Recently, DIXI Medical (Besancon, France) became an FDA-approved manufacturer stereotactic electrophysiology (SEEG) depth electrodes that can record from single units. This electrode variant is novel in both surgical and analytic techniques compared to other depth electrodes used for single-unit analyses (i.e., described in Minxha et al., 2018). Thus, the aims of the current study are to describe and

discuss the methodologies surrounding the use of DIXI Medical Microdeep® Micro-Macro depth electrodes (DIXI MME) that have the capability to record from single neurons in cognitive neuroscience research. Implantation techniques unique to this electrode and useful for others interested in this research will be detailed to allow for replication by other groups. Furthermore, OSort, a semi-automatic spike sorting program (Rutishauser, 2021), was modified for single unit analyses with DIXI MMEs; the modifications of which will be detailed for replication by other groups as well. To demonstrate the utility of DIXI MMEs with a real-world example, we implemented these electrodes to advance the understanding of episodic memory. We were afforded a rare opportunity to record eye movements and activity from single neurons from the medial temporal lobe in humans during the encoding and retrieval process. Patients with medically refractory epilepsy (N=4, M_{age} = 41.5 ±8, 75% female) admitted for intracranial monitoring of seizure activity via SEEG depth electrodes completed the study during their inpatient stay in the Epilepsy Monitoring Unit at University of Colorado Hospital. Patients were implanted with 1 DIXI MME in either the hippocampus or amygdala to record single neuron activity. Eye movements were recorded binocularly from a desktop mounted EyeLink 1000 Plus System (SR Research, Canada) while patients completed a computerized episodic memory paradigm. Using cognitive and computational models to relate both behavioral performance and eye tracking processes to the underlying neural mechanisms will ultimately inform the design of targeted interventions for causal disruptions in these systems.

Disclosures: M.L. Darwin: None. **J. Zheng:** None. **U. Rutishauser:** None. **S. Ojemann:** None. **D.R. Kramer:** None. **J.A. Thompson:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.24/XX59

Topic: I.07. Data Analysis and Statistics

Support: A*STAR Grant RIE2025

Title: A Pose-Informed De-Noising Diffusion Model for Infant and Adult Naturalistic EEG Signals

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Abstract: Artifact contamination in EEG signals poses a persistent challenge, owing to the diverse sources of artifacts (including ocular, muscular, sweat, and electrical), which exhibit limited commonalities among individuals. These challenges are amplified when EEG data is collected under naturalistic settings permitting free movement in paediatric and adult

participants. Existing denoising methods, such as Independent Component Analysis assume linearity between artifact and artifact-contaminated EEG signals. Also, the quality of the clean signal extracted from such methods is contingent on the dominance of one noise source over others. These assumptions are not always held, leading to poor noise segregation. Further, existing EEG cleaning methods require subjective judgments to label noise components, often without the aid of objective ground truth data. To address these issues, we present a new EEG-denoising model that is able to utilise body pose data to perform more effective denoising of movement-contaminated EEG signals and is therefore suitable for application with naturalistic EEG datasets. Our contribution is twofold: 1) we introduce ground truth constraints from - pose coordinates - extracted from the participant's video data and represented as x and y coordinates of 25 body keypoints (e.g., wrists, eyes, ankles) to guide the denoising process and 2) a denoising diffusion model (Song et.al 2021) (EEG_DDM) which takes both the artifact contaminated EEG and pose coordinates as input to denoise the EEG signal. To ensure generalisability, the model accommodates denoising scenarios both with and without pose coordinates and is thus applicable for common EEG datasets without pose coordinates. Experiments on adult EEG demonstrate that the model achieves a cosine similarity of nearly 0.85 to the ground truth data when utilising pose coordinates and still maintains a similarity ~ 0.80 in the absence of pose data. Furthermore, our model performs comparably to the current automated state of the art methods such as ICLabel (Tonachini et.al 2020), RELAX (Bailey et.al 2022), EEGDenoiseNet (Zhang et.al 2022) and GANS (Brophy et.al 2022).

Disclosures: A. Dutta: None. **M.H. Andre:** None. **L. Covarrubias:** None. **S. Georgieva:** None. **C. Gerloff:** None. **B. Li:** None. **V. Leong:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.25/XX60

Topic: I.07. Data Analysis and Statistics

Support: Japan Society for the Promotion of Science(JSPS) KAKENHI Grant Number JP22K21225

Title: Improvement of accuracy in predicting subacute stroke functional outcome by machine learning with increased clinical indicators: A retrospective study

Authors: *Y. MIYAZAKI[1,2,3], M. KAWAKAMI[3,2], K. KONDO[2,3], M. TSUJIKAWA[2,3], K. HONAGA[4,2], K. SUZUKI[5], T. TSUJI[3];
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Abstract: The prognosis of post-stroke functional recovery is important in early hospitalization because the Activities of Daily Living (ADL) of stroke patients affect the lives of patients and their caregivers after discharge. Many previous studies reported improved prediction accuracy by adding various clinical findings to Multiple Linear Regression analyses (MLR). However, the prediction accuracy of stroke patients, which is nonlinear data, may have decreased by MLR, which assumes linear data. Therefore, the purpose of this study is to examine whether the prediction accuracy can be improved by using machine learning, which can analyze nonlinear data. We also examine whether prediction accuracy can be improved by adding clinical indicators as explanatory variables.In this study, 980 participants who met the inclusion and exclusion criteria were included, and prognostic models were developed using the total Functional Independence Measure (FIM) motor scores at discharge as the objective variable. From the Electronic Health Record, age, number of days from onset to admission day, and FIM at admission were collected and used as explanatory variables to develop prediction models. In addition, prediction models were also developed by adding the Stroke Impairments Assessment Set (SIAS), grip strength, Body Mass Index (BMI), and Geriatric Nutritional Risk Index (GNRI) as explanatory variables. Decision trees (DT), Ensemble Learning (EL), Support Vector Regression (SVR), Artificial Neural Network (ANN), and Gaussian Process Regression (GPR) were adopted as machine learning in addition to the conventionally used MLR. The coefficients of determination were used as prediction accuracies and compared.The coefficients of determination for prognosis based on patient background and FIM at admission were 0.69 for MLR and 0.75 for GPR; when clinical findings such as SIAS were added, the coefficients of determination improved to 0.72 for MLR and 0.77 for GPR.This study suggested that GPR may improve prediction accuracy more than MLR. In addition, the prognostic model with the addition of SIAS and GNRI was more accurate than the prognostic model based on patient background and FIM at admission.

Disclosures: Y. Miyazaki: None. **M. Kawakami:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); INTEP. **K. Kondo:** None. **M. Tsujikawa:** None. **K. Honaga:** None. **K. Suzuki:** None. **T. Tsuji:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.26/XX61

Topic: I.07. Data Analysis and Statistics

Support: National Natural Science Foundation of China Grant 32200921

Title: Genetic and cellular decoding of cortical region and its association to psychiatric disorders

Authors: *Y. ZHAN, C. LIU;
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Abstract: The spatial distribution of cell types is critical in determining their functional properties and has significant implications for understanding psychiatric disorders. However, the regional cellular composition in the neocortex and its association to genetic risks for psychiatric disorders remains largely unknown. In this study, we first integrated brain-wide microarray gene expression data from Allen Human Brain Atlas (AHBA) with single-nucleus (sn) RNA-sequencing data to attribute expression-driven cell types to specific regions. We then examined whether illness-related genes are more prevalent in regions where specific cell types are preferentially localized. Our results reveal that the neocortex can be divided into sensory, anterior association and posterior association subgroups, with each subgroup comprising similar constituent cells. The sensory subgroup, encompassing the primary visual cortex, somatomotor cortex and posterior cingulate cortex, shows a preferential expression of excitatory neuronal subclasses and parvalbumin interneurons in the granular layer (layer 4). The posterior association subgroup, encompassing the lateral, ventrolateral prefrontal cortex, and posterior association cortex, exhibits a preferential expression of excitatory neuronal subclasses in the spuragranular (layers 1-3) and granular layers. In contrast, the anterior association subgroup, comprising the anterior association cortex, demonstrates a preferences of glia cells and excitatory subclasses in the infragranular (layers 5 and 6), along with excitatory and inhibitory subclasses in the supragranular layer. The regional distribution of neuronal cell types was correlate with the cortical layer-specific thickness. The granular layer neuronal subtypes-dominant sensory and posterior association subgroup regions tend to have a relative thicker granular layer. Conversely, the anterior association subgroup regions, dominated by infragranular and supragranular layer neuronal subtypes, exhibits thicker supargranular and infragranular layers. Additionally, by integrating psychiatric disorder-associated gene sets, we find the anterior association subgroup region exhibited enrichment for up-regulated and primary sensory cortex exhibited enrichment for down-regulated genes associated with autism spectrum disorder, bipolar disorder and schizophrenia. These findings advance our understanding of the cellular underpinnings of brain functional specialization and the neural basis of psychiatric disorders, potentially paving the way for the development of more targeted and effective treatments.

Disclosures: **Y. Zhan:** None. **C. Liu:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.27/XX62

Topic: I.07. Data Analysis and Statistics

Support: Alzheimer's Association Grant (AARG-22-972541)

Title: Contrastive graph representation learning of brain functional networks improves prediction of CSF amyloid-beta in Alzheimer's disease

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Abstract: Contrastive graph representation learning of brain functional networks improves prediction of CSF amyloid-beta in Alzheimer's disease

Authors: Kanhao Zhao[1], Ricardo Osorio[2], Yu Zhang[1,3*1] Department of Bioengineering, [2] Department of Electrical and Computer Engineering, Lehigh University, Bethlehem, PA, USA[2] Department of Psychiatry, New York University Grossman School of Medicine, New York, NY, USA* Corresponding author: Email: yuzi20@lehigh.edu

Disclosures: K. Zhao: None. R. Osorio: None. Y. Zhang: None.

Abstract: Contrastive learning has shown significant promise in distinguishing the representative variants between the background and target datasets. However, existing contrastive strategies were not specifically designed for graph data, limiting the utilization of the topological information. In this study, we proposed a novel framework, Contrastive Graph Variational Autoencoder, tailored for graph data-based contrastive learning. We aim to fully utilize the topological information in brain functional graphs to identify target-specific salient latent features from target dataset, contrasting the background shared features. Moreover, we introduce a prediction loss to enhance the predictive ability of the target-specific latent features, ensuring they correlate with clinical scores. Cerebrospinal fluid (CSF) levels of amyloid-beta is a crucial biomarker for drug development of Alzheimer's disease (AD) and categorizing neurodegenerative conditions. The relationship between brain dysfunction and the accumulation of amyloid-beta pathology remains unclear. We aim to utilize brain functional connectivity graphs to shed light on this association. Specifically, we extracted the resting-state function connecitivity graph from healthy controls and the patients with Alzheimer's disease from the Alzheimer Disease Neuroimaging Initiative dataset and PResymptomatic EValuation of Experimental or Novel Treatments for AD dataset. Then employing brain functional connectivity features from healthy subjects as the background and Alzheimer's disease as the target, we demonstrate the superiority of our model in predicting CSF amyloid-beta, compared to other state-of-the-art approaches. Further investigations indicated that the Alzheimer's disease-specific features and the healthy-shared features decomposed by our model are significantly distinguishable. This indicates that our model successfully disentangle the disorder-specific representations for Alzheimer's disease from healthy-control-shared representations, providing valuable insights into the neurobiological characteristics of the disease.

Disclosures: K. Zhao: None. **R.S. Osorio:** None. **Y. Zhang:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.28/XX63

Topic: I.07. Data Analysis and Statistics

Support: 5UH3NS119844
5R01NS096008

Title: Analysis of Chronic Recordings in Centromedian Thalamus and Globus Pallidus Interna for Closed Loop Deep Brain Stimulation in Tourette Syndrome

Authors: *J. GOMEZ[1], G. LOWOR[1], K. FOOTE[1], M. S. OKUN[1], A. GUNDUZ[2];
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Abstract: Tourette Syndrome (TS) is a neuropsychiatric disorder characterized by repetitive and involuntary motor and phonic tics. Deep Brain Stimulation (DBS) has shown promise as a therapeutic option for refractory TS, particularly in alleviating motor tics. This study explores the identification of targets of tic detection and suppression in the Centromedian (CM) Nucleus of the Thalamus and the Anterior Globus Pallidus Interna (aGPi) using closed-loop DBS. The study spans nine months, comprising several phases: identifying the best nuclei for tic detection and suppression, optimizing adaptive settings, and testing the optimized settings. Data collection involves rest periods, voluntary movement of hands upon cue presentation, and periods of tics while recording video and streaming data from the Medtronic Percept implants and Delsys Wearable Sensors. The recorded data is aligned and marked for analysis, comparing Local Field Potential (LFP) power and time domain data recordings during different conditions. The study involves eight subjects, with one patient fully implanted at present. Our preliminary results are from a female subject with bilateral DBS electrodes targeting CM and aGPi, and bilateral Percept Neurostimulators. Our analysis reveals that lower frequency bands (1-10 Hz) show consistent separability of tics from rest for this subject (p-value < 0.1). However, due to hardware limitations, the lowest observable range for closed-loop DBS is 7.81 ± 2.5 Hz. Despite this constraint, we have successfully initiated closed-loop DBS using the LFP signal. Future directions include periodic evaluation of stimulation thresholds to maintain therapeutic efficacy, prevent subject habituation, and improve closed-loop DBS parameters optimization techniques based on real-time and chronic monitoring of neural activity and symptom progression. Additionally, investigating the impact of CM and aGPi stimulation on TS-associated psychiatric comorbidities is crucial. While the first subject does not present with psychiatric comorbidities, future subjects will shed light on the effects of DBS on these conditions. Lastly, we aim to explore alternative approaches for efficient tic detection and marking during patient visits, as the current video labeling technique is time-consuming. In conclusion, our study demonstrates the potential of closed-loop DBS targeting CM or aGPi for TS treatment. Further research is needed to optimize DBS parameters and monitor symptom progression, ultimately leading to tailored therapies that account for individual patient characteristics.

Disclosures: J. Gomez: None. **G. Lowor:** None. **K. Foote:** None. **M.S. Okun:** None. **A. Gunduz:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.29/XX64

Topic: I.07. Data Analysis and Statistics

Support: Institute of Information & Communications Technology Planning & Evaluation (IITP)/Korean Government (MSIT) Grant 2017-0-00432

Title: An Error-Correction for Augmented Reality Based Steady State Visually Evoked Potential to Improve Information Transfer Rate

Authors: *J. HA[1], S. PARK[2], H. JANG[1], L. KIM[1,3];
[1]Bionics Res. Ctr., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Industry-Academy, [3]Dept. of HY-KIST Bio-Convergence, Hanyang Univ., Seoul, Korea, Republic of

Abstract: Nowadays, augmented reality (AR) devices enable portable steady-state visually evoked potential (SSVEP) experiments by presenting visual stimuli wherever the user is. However, users' gaze remains within the stimulus field because the visual stimuli in AR follow head movement. Inconvenience caused by wearing AR devices and fatigue resulting from continuous visual stimuli could lead to low accuracy and low information transfer rate (ITR) for SSVEP. Recently, many researchers have conducted AR-based SSVEP studies to improve performance. However, none of these studies have considered the components or situations on SSVEP errors. In this study, we aimed to increase the ITR by applying an error correction, unlike previous studies that focused on improving algorithms to increase accuracy and ITR or reducing window time to increase ITR. Seven subjects of both genders (3 males, 4 females; mean age: 24.6 ± 2.3 years) participated in this experiment. EEG data were recorded using a 64-channel Brain Vision actiChamp. All subjects wore an EEG cap with Microsoft Hololens 2, stood up, and performed the experiment for SSVEPs every 4 seconds for a total of 100 times using flickering visual stimulation under 4 target frequencies (6.6, 7.5, 8.57, 10 Hz). EEG data acquired from eight occipital electrodes were selected for SSVEP classification. In this study, SSVEP classification adopted an extended multivariate synchronization index (EMSI) algorithm, which calculates the synchronized index between EEG signals and reference signals and applies time-delay embedding to the EEG data. Regarding the error correction strategy, we hypothesized that participants would gaze at the target correctly. If error trials with similar synchronization indexes occurred, it was considered that participants did not gaze at the target correctly. We used 4 seconds of data for EMSI, and this time range was used to determine the original accuracy and ITR. On the other hand, the ITR for corrected trials was based on 5 seconds (time range [4 seconds] + error recognition time [1 second]). The original accuracy and ITR were 89.07% and 25.83 bits/min, respectively, while the corrected accuracy and ITR were 94.71% and 31.80 bits/min, respectively. We hypothesized that cases where the synchronization index on the target was not the highest occurred due to delayed onset time in gazing at the target or the effect of flickering light from other targets. In future studies, the inclusion of an eye-tracking device would allow for a more accurate analysis and the development of more effective error correction methods for all trials, unlike the current study.

Disclosures: **J. Ha:** None. **S. Park:** None. **H. Jang:** None. **L. Kim:** None.

Poster

PSTR311. Data Analysis and Statistics: MRI, EEG, MEG, Clinical Neuroscience

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR311.30/XX65

Topic: I.07. Data Analysis and Statistics

Support: CONACYT Grant 252808 for Gonzalo Flores
CONACYT Estancias Posdoctorales por México Grant 662350 for Hiram Tendilla-Beltrán

Title: Covid-19 prevalence is modified by specific diagnoses and antipsychotic exposure in psychiatric patients

Authors: *H. TENDILLA-BELTRÁN[1], Á. RIVAS-RAMÍREZ[2], F. FLORES[2], L. CARBAJAL-RIMOLDI[2], L. GÓMEZ-MENDOZA[2], G. LOAIZA[2], G. FLORES[1,2];
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Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the biological agent for Coronavirus disease 2019 (COVID-19), has brain tropism and induces neuroinflammation, which also is a core mechanism of psychiatric disorders such as schizophrenia, depression, and bipolar disorder. In this sense, patients diagnosed with psychiatric diseases seem to be vulnerable to COVID-19 outcomes. Interestingly, some drugs employed for the treatment of psychiatric diseases, including antipsychotics, have anti-inflammatory and antioxidant properties, suggesting that they can be protecting the brain against neuroinflammation. The clinical records of 170 inpatients were analyzed during the COVID-19 outbreak (June-September 2020) and a year followed up, to determine the effects of sex, age, psychiatric/neurological diagnosis, comorbidities, and antipsychotic exposure on COVID-19 prevalence. The prevalence of COVID-19 in hospitalized patients with psychiatric disorders was increased compared with that of the general population; however, a lower mortality rate was detected. Furthermore, inpatients with intellectual disabilities had higher COVID-19 prevalence (OR 2.2, 95% CI: 0.2-0.8; P = .0434) than those with schizophrenia, which was lower (OR 0.4, 95% CI: 0.2-0.8; P = .0250). Regarding antipsychotic effects, inpatients exposed to first-generation drugs (FGA) have reduced COVID-19 prevalence, specifically in the group of 18-65 years of age (OR 0.37, 95% CI: 0.17-0.81, P = 0.0202) and diagnosed with intellectual disabilities (OR 0.23, 95% CI: 0.16-0.55, P = 0.0039). While the second-generation antipsychotics increased COVID-19 prevalence in the general hospital population (OR 2.11, 95% CI: 1.13-3.86, P = 0.0207), in inpatients 18-65 years of age (OR 2.38, 95% CI: 1.2-4.92, P = 0.0156) and in inpatients diagnosed with intellectual disabilities (OR 2.87, 95% CI: 1.3-6.19, P = 0.0108). Also, reduced Long COVID prevalence, in comparison with the general population, was detected in these inpatients. These results indicate that the prevalence of COVID-19 in hospitalized patients with psychiatric disorders is modified by multiple factors including the specific diagnosis and the presence of comorbidities. Additionally, FGA seemed to have protective effects against COVID-19 effects, including long-term ones. Our data greatly advance the body of information regarding how antipsychotics alter COVID-19 outcomes, albeit

preliminary, in which their antiviral, antioxidant, and anti-inflammatory properties also impact the pathophysiology of psychiatric diseases.

Disclosures: H. Tendilla-Beltrán: None. **Á. Rivas-Ramírez:** None. **F. Flores:** None. **L. Carbajal-Rimoldi:** None. **L. Gómez-Mendoza:** None. **G. Loaiza:** None. **G. Flores:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.01/XX66

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01 DK120824
NIH U01 NS113873

Title: Blocking Aδ- and C-fiber neural transmission by sub-kilohertz peripheral nerve stimulation

Authors: *S. ZHANG, L. CHEN, J. LIU, A. SEFERGE, B. FENG;
Univ. of Connecticut, Storrs, CT

Abstract: Peripheral nerve stimulation (PNS) has emerged as a non-drug alternative for managing chronic pain and other neurological disorders. The pain-managing effect of PNS is usually attributed to the activation of myelinated A-fiber afferents, which causes a non-painful tingling sensation known as paresthesia that masks the pain sensation from the same area. We recently showed that sub-kilohertz electrical stimulation of the dorsal root ganglia (DRG) reversibly blocks afferent transmission via activity-dependent conduction slowing. In this study, we further investigated whether electrical stimulation of the peripheral nerve trunk can also cause neural transmission block. To that end, we explored the mechanisms and parameters of PNS to block axonal neural transmission by conducting *ex vivo* single-fiber recordings from harvested mouse sciatic, saphenous, and vagal nerves. In a two-compartment tissue chamber, we evoked action potentials from one end of the harvested nerve in the tissue chamber perfused with Krebs solution and conducted single-fiber recordings from split nerve filaments approximately 20 μm thick in the adjacent recording chamber filled with paraffin oil. PNS was delivered in the middle of the nerve trunk using a glass suction electrode at frequencies of 10, 50, 100, 500, and 1000 Hz. Similar to DRG stimulation, suprathreshold PNS reversibly blocks axonal neural transmission of thinly myelinated Aδ-fibers with a conduction velocity (CV) of 1-4 m/s and unmyelinated C-fibers with a CV less than 1 m/s. PNS leads to a progressive decrease in CV until transmission blockage, suggesting activity-dependent conduction slowing. The blocking efficiency is dependent on the axonal conduction velocity, with Aδ-fibers efficiently blocked by 50-100 Hz stimulation, while C-fibers are blocked by 10-50 Hz. This frequency-dependent blocking effect is consistently observed in the sciatic, saphenous, and vagal nerves. The current study provides direct evidence of reversible Aδ- and C-fiber transmission blockage by low-

frequency (<100 Hz) electrical stimulation of the nerve trunk, a previously overlooked mechanism that can be harnessed to enhance the therapeutic effect of PNS.

Disclosures: S. Zhang: None. **L. Chen:** None. **J. Liu:** None. **A. Seferge:** None. **B. Feng:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.02/XX67

Topic: I.08. Methods to Modulate Neural Activity

Support: NRF-2022R1I1A4063209
2022R1A2C2005062

Title: Vagus nerve stimulation for EEG modulation in rats

Authors: *Y. LEE[1], S.-Y. MOON[2,3], J. SUNG[4], S. JUN[2,5];
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Abstract: Recently, vagus nerve stimulation (VNS) has been studied as a therapy for various diseasesincluding epilepsy, depression, cardiovascular illness, obesity, diabetes, and traumatic brain injury.The treatment effects are attributed to the widespread connections of vagus nerves. Since VNSalso regulates the autonomic nerve system, it is well known that heart rate can be modulated byVNS application. In addition, the possibility of improving cognitive function is suggested, andprior studies have shown that norepinephrine and dopamine levels have increased in the frontallobe (cognitive integrated center) and hippocampus (memory center) . In this study, we aim toverify which brain regions and which frequency bands of EEG are affected by VNS in the rat brain.Along with heart rate recording, EEG power spectrums are obtained in different brain regions(both left and right medial prefrontal cortex (mPFC) , somatosensory (S1) , and parietal associationcortex (PtA)) when various stimulation frequencies are applied on vagus nerve of Sprague-Dawleyrats. For VNS, a bipolar cuff electrode was wrapped around the vagus nerve and connected to acurrent stimulator. When it was ON for 1sec, biphasic current square pulses (amplitude: 0.8mA;width: 0.8ms; frequency: 1, 10, 30, 60Hz) were delivered under light isoflurane anesthesia. EEGpower spectrums was analyzed for each stimulation frequency. As a result, this study confirmedthat VNS can modulate brain EEG signal and identified the most effective stimulation frequencyfor modulating brain signals.

Disclosures: Y. Lee: None. **S. Moon:** None. **J. Sung:** None. **S. Jun:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.03/XX68

Topic: I.08. Methods to Modulate Neural Activity

Support: CBBS NeuroNetwork 17

Title: Unlocking the Potential of Transcutaneous Vagus Nerve Stimulation: Circuit-Inspired Approaches for Locus Coeruleus Activation and Noradrenergic Modulation

Authors: *K. MORE[1], C. GONZÁLEZ-CABRERA[1,2], A. M. JARAMILLO[1], M. BETTS[3], M. PRIGGE[1,2,4];
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Abstract: One-Sentence-Summary: Transcutaneous stimulation of the auricular branch of the vagus nerve induces a stimulation-locked increase in firing rate in noradrenergic brain stem neurons, which persists for an extended period.Non-invasive electrical stimulation offers a sophisticated method to selectively manipulate neuronal circuits with greater accuracy and spatial resolution compared to pharmacological interventions. Transcutaneous Vagus Nerve Stimulation (taVNS) has the potential to activate specific neuronal circuits, leveraging our understanding of the neural circuitry that has emerged in recent years. The auricular branch of the Vagus Nerve, which innervates the inner ear, serves as a gateway to various neuromodulatory networks that exert significant control over sensory, spatial, and higher cognitive cortices. However, the exact connectivity between the auricular branch of the vagus and brainstem nuclei, such as the Locus Coeruleus (LC) and Dorsal Raphe, remains unclear. It is believed that auriculo-vagal afferents converge in the nucleus of the solitary tract, which has an excitatory connection to the LC via the nucleus paragigantocellularis, thereby activating the ascending LC-NA system. However, there is a lack of systematic studies investigating how specific stimulation parameters at the ear level translate into the activation of the LC.
Therefore, we conducted taVNS experiments in anesthetized mice to engage the LC-NA system and study stimulation parameters that can maximize activation in the LC. Initially, we measured cFos activity in the LC and peri-LC regions after administering taVNS at the cymba concha or the outer ear, using both high and low current regimes. The mice were stimulated for 15 minutes with a duty cycle of 30s ON and 60s OFF. Acute taVNS resulted in a significant increase in cFos-positive neuronal density in the LC bilaterally, compared to the sham groups, under both stimulation regimes (unpaired t-test). We consistently observed cFos-positive neurons in close proximity to the medial LC region.
Next, we aimed to map the stimulation parameters to the activation of individual LC neurons with higher temporal and spatial resolution. To achieve this, we employed the juxtacellular recording-labeling technique to monitor the activity of a single LC neuron during taVNS. We observed increased firing activity in the neuron during the stimulation bouts (parameter-free

ZETA-test), with a spike latency of 15-20ms following pulse delivery. Additionally, we noted an increased effectiveness of stimulation after several repeated stimulation bouts. The responsive neurons did not exhibit any topographic bias within the LC.

Disclosures: **K. More:** A. Employment/Salary (full or part-time):; Leibniz Institute for Neurobiology, Magdeburg. **C. González-Cabrera:** A. Employment/Salary (full or part-time):; Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD, USA. **A.M. Jaramillo:** A. Employment/Salary (full or part-time):; Leibniz Institute for Neurobiology, Magdeburg. **M. Betts:** A. Employment/Salary (full or part-time):; Institut für Kognitive Neurologie und Demenzforschung, Magdeburg. **M. Prigge:** A. Employment/Salary (full or part-time):; Leibniz Institute for Neurobiology, Magdeburg, Center for Behavioral Brain Sciences, Magdeburg, Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD, USA.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.04/XX69

Topic: E.05. Brain-Machine Interface

Title: Evaluating targeted stimulation patterns for artificial sensory feedback with in-silico rodent dorsal column model

Authors: *R. RADHAKRISHNA[1], A. P. YADAV[2];
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Abstract: Spinal cord stimulation (SCS) has evolved from its original purpose as a treatment for chronic pain, to a means of restoring motor function in individuals with spinal cord injury (Miller et al., 2016). SCS also holds promise in delivering sensory feedback to the cortex via activation of the dorsal column pathways (Yadav & Nicolelis, 2017). Studies have successfully generated artificial sensations in rats and primates via SCS (Yadav et al., 2021, Slack et al., 2022). However, optimal stimulation parameters to reliably induce biomimetic sensory feedback are yet unknown (Formento et al., 2020), limiting clinical translation. Numerical methods and biophysical models provide an opportunity to simulate stimulation parameters and study their impact on neural structures. We coupled finite element (FE) simulations with the Izhikevich model, to explore how axons behaved under different stimulation conditions (Izhikevich, 2003). This approach allowed us to rapidly simulate and study different stimulation patterns. A CAD model of the rat spinal cord was created from *The Spinal Cord* atlas in Shapr3D (Watson et al., 2009). The modelled bodies included extradural tissue, neuronal tissue, electrodes, and 850 axons randomly distributed in dorsal column. Two stimulation patterns varying in periodicity were simulated for five seconds. Five axons were randomly selected for the simulation using the Izhikevich model generated in MATLAB. Stimulation involved biphasic, bipolar current

injection of 350uA. This was delivered firstly as a periodic pulse train at 50Hz for two seconds, followed by an aperiodic pulse train generated from a gamma distribution with mean frequency of 50Hz. The stimulation period comprised 100 pulses for both patterns, followed by three seconds with no stimulus. The axons reacted differently to the simulated pattern injection. For pattern 1 (periodic 50Hz), the total number of spikes elicited was 64. For the aperiodic pattern, the number of spikes across all axons totaled 85. There was a change in the activity of axons #2, 4 and 5. By coupling established numerical methods, we have demonstrated that temporally different stimulation patterns influence spiking activity. The difference in response to the patterns may influence how sensory information is transmitted to the cortex. Apart from unit activity, there is also a prospect to study peak-to-peak voltages, excitatory and inhibitory behavior between neighboring axons, etc. Comparative analysis between the various stimulation parameters will allow us to identify potential candidate patterns that can then be tested in-vivo to specifically provide biomimetic sensory feedback for individuals with SCI.

Disclosures: R. Radhakrishna: None. **A.P. Yadav:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.05/XX70

Topic: E.05. Brain-Machine Interface

Support: NIH Award Number K01NS127936
Washington University's McDonnell Center for Systems Neuroscience Small Grants Program

Title: Efficiency of high-frequency modulated stimulation waveforms in sensory and motor pathways

Authors: *R. KEESEY[1], L. LOMBARDI[1], R. HAWTHORN[1], N. BRYSON[1], U. HOFSTOETTER[2], K. MINASSIAN[2], I. SEÁÑEZ[1];
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Abstract: Spinal cord injury (SCI) leads to permanent motor function loss and reduced autonomy for approximately 12K individuals in the United States each year. Transcutaneous spinal cord stimulation (tSCS) has emerged as a promising non-invasive technique for restoring residual function post-injury. However, potential discomfort associated with the high stimulation amplitudes necessary for producing strong muscle contractions for an orthotic effect poses a critical barrier to its clinical translation. To mitigate this issue, some applications of tSCS have advocated the use of 5-10 kHz high-frequency modulated waveforms that are believed to reduce discomfort during stimulation. However, emerging evidence suggests that these high-frequency

modulated waveforms do not offer greater tolerability compared to conventional stimulation when adjusted for motor response amplitudes. Additionally, the neural mechanisms underlying the recruitment of motor and sensory fibers by high-frequency waveforms remain poorly understood. This study aimed to investigate the neural mechanisms of recruitment for high-frequency stimulation in afferent and efferent fibers through peripheral nerve stimulation. We hypothesized that high-frequency stimulation would be less efficient at recruiting sensory and motor fibers than conventional waveforms. Furthermore, we hypothesized that high-frequency waveforms would rely on temporal summation processes to elicit muscle responses and exhibit preferential recruitment of motor efferent pathways over proprioceptive afferents. Tibial nerve stimulation was used to evoke H-reflexes and M-waves recorded at 50 kHz in the soleus muscle of neurologically intact participants to analyze the recruitment of proprioceptive afferent and motor fibers, respectively. We describe the stimulation responses of motor and sensory pathways, providing insights into the distinctive recruitment characteristics of conventional and high-frequency modulated waveforms. By focusing on peripheral nerve stimulation, this study offers a simplified system to examine the recruitment mechanisms of tSCS while allowing for the direct analysis of H reflexes and M waves, which appear as separate potentials in the EMG recordings. These results contribute to the understanding of high-frequency stimulation in SCI rehabilitation, promoting the translation of tSCS to further enhance and accelerate recovery.

Disclosures: **R. Keesey:** None. **L. Lombardi:** None. **R. Hawthorn:** None. **N. Bryson:** None. **U. Hofstoetter:** None. **K. Minassian:** None. **I. Seáñez:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR312.06/XX71

Topic: E.05. Brain-Machine Interface

Title: Decoding high-density supraspinal representation of spatial and spatiotemporal patterns of spinal cord stimulation

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Abstract: A promising method of providing sensory feedback to neuroprosthetic devices and brain-computer interfaces (BCIs) is spinal cord stimulation (SCS). However, the relationship between evoked supraspinal response and temporal, spatial, or spatiotemporal parameters of SCS is not well understood, limiting the ability to generate naturalistic sensory feedback. Investigating whether SCS parameters can be decoded from evoked response is critical for developing a neuroprosthesis that induces reliable and reproducible sensory percepts. Here, we examined brain responses to spatial/spatiotemporal SCS patterns using high-density recordings and developed deep neural network (DNN) models which classify evoked responses to these

SCS patterns. 5 anesthetized rats were implanted with a Neuropixel probe and a 16-channel electrode array. The probe targeted the somatosensory cortex (S1) and the ventral posterolateral thalamic nucleus (VPL), allowing for local field potential and action potential (AP) recording on 384 channels acquired by SpikeGLX. The electrode array was positioned epidurally at the thoracic level and used the Ripple Neuro Scout processor and Trellis software to control SCS. A MATLAB interface controlled SpikeGLX and Trellis to simultaneously record brain activity and deliver SCS. During recordings, 1-1.2 sec biphasic/bipolar pulse-trains were delivered at 15 unique cathodes while anode was kept constant (spatial variation) and 10 unique anode-cathode patterns (spatiotemporal variation). Spike sorting of AP recordings was performed using *ecephys spike sorting* which incorporated *Kilosort2* and curated in *phy*. To train DNN models, peristimulus time histograms (PSTHs) were generated in MATLAB using the first pulse of each SCS pulse-train. Two DNNs were developed in Python following convolutional architecture to learn both time- and depth-dependent features of the neural recordings. Models were evaluated using 5-fold cross validation. The DNN trained on neural response to spatial variation (15 classes) had testing accuracy of 66.56 ± 4.51% and training accuracy of 85.08 ± 2.39%. The DNN trained on neural response to the 10 spatiotemporal patterns, achieved testing accuracy of 83.14 ± 2.97% and training accuracy of 98.46 ± 1.25%. These results demonstrate that SCS modulates neural activity in S1 and VPL. DNN models learned to effectively classify evoked responses, highlighting that spatial/spatiotemporal patterns of SCS can be decoded from supraspinal responses. SCS can be an effective method to transmit sensory information to the brain and generate sensory feedback that can be optimized by manipulating spatial/spatiotemporal parameters.

Disclosures: **J. Slack:** None. **A. Yadav:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.07/XX72

Topic: E.05. Brain-Machine Interface

Support: NIH Award Number K01NS127936
Washington University's McDonnell Center for Systems Neuroscience Small Grants Program

Title: Enhanced selectivity of transcutaneous spinal cord stimulation by multielectrode configuration

Authors: *N. K. BRYSON, L. LOMBARDI, R. HAWTHORN, J. FEI, R. KEESEY, J. PEIFFER, I. SEÁÑEZ;
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Abstract: Enhanced Selectivity of Transcutaneous Spinal Cord Stimulation by Multielectrode Configuration

***Noah Bryson[1,2]**, Lorenzo Lombardi[1,2], Rachel Hawthorn[1,2], Jie Fei[1,2], Rodolfo Keesey[1,2], J.D. Peiffer[1,2], Ismael Seáñez[1,2,41] Biomedical Engineering, Washington University in St. Louis[2] Division of Neurotechnology, Washington University School of Medicine in St. Louis[3] Neurosurgery, Washington University School of Medicine in St. Louis

Spinal Cord Injuries (SCI) are devastating events impacting sensory, motor, and autonomic nervous function caudal to these lesions. Spinal cord stimulation (SCS) has emerged as an effective tool to aid in the restoration of motor function. A barrier to translation of spinal cord stimulation is the highly invasive nature and cost of implanted systems, coupled with the low functional selectivity of transcutaneous SCS (tSCS). Our study aims to enable simultaneous rostrocaudal and unilateral selectivity of tSCS in leg muscles by one electrode configuration. We hypothesize that using a multi-electrode array placed over the lumbosacral spinal cord will enhance the selectivity of tSCS conventional tSCS. A single electrode and the multi-electrode array were placed centered over the T11/T12 interspinous ligament. Paired biphasic pulses of increasing amplitude were delivered through the single and each multi-electrode to elicit evoked responses in the rectus femoris (RF), semitendinosus, vastus lateralis (VL), tibialis anterior (TA), medial gastrocnemius and soleus (SL) muscles. EMG sensors were placed on each muscle to record responses (fs: 2000 Hz). Selectivity was calculated from the recruitment curves generated by the stimulation sweep. Nineteen neurologically intact individuals and two individuals with SCI took part in this study. Simultaneous rostrocaudal and ipsilateral selectivity of tSCS increased significantly with multi-electrode tSCS in the RF, VL, TA and SL. We found significant post-activation depression across all neurologically intact subjects, verifying that multi-electrode tSCS is mediated by the posterior root muscle (PRM) reflex. In individuals with spinal cord injury, multi-electrode tSCS enabled the recruitment of muscles that were unable to be recruited by the single electrode configuration. Multi-electrode tSCS enables significantly higher selectivity than conventional tSCS in neurologically intact individuals and allows for an enhanced profile of stimulation targets in individuals with SCI. The reflex pathway enabling these effects suggests a promising path to translation that allows the interaction between stimulation effects and residual neural inputs in people with SCI.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.08/XX73

Topic: E.05. Brain-Machine Interface

Support: NIH Award Number K12HD073945
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Title: Short-term changes in neural excitability of cortico-reticulo-spinal circuits induced by spinal cord stimulation and activity-based training

Authors: *R. HAWTHORN, H. NIE, R. KEESEY, L. LOMBARDI, I. SEÁÑEZ;
Biomed. Engin., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Spinal cord injuries (SCI) lead to long-lasting paralysis, affecting hundreds of thousands of individuals in the United States. When combined with training, spinal cord stimulation (SCS) has been shown to induce significant functional improvements in individuals with SCI. However, the neural mechanisms that mediate this neurorecovery remain poorly understood. This study aims to quantify short-term changes in neural excitability of the corticospinal, reticulospinal, and spinal motoneurons induced by transcutaneous SCS and activity-based training, both independently and in combination. We used transcranial magnetic stimulation (TMS) to record motor evoked potentials (MEPs) to examine the contributions of the corticospinal tract, the StartReact response (a shortening in response time after a startling auditory cue) for the reticulospinal tract, and F-wave responses in the soleus to tibial nerve stimulation for the spinal motoneuron tract. Pre- and post-evaluations were conducted after three distinct 30-minute training sessions: activity-based training; SCS only; and a combination of activity-based training and SCS. Activity-based training involved a non-invasive body-machine interface (BoMI), where participants used their legs to control a 2D cursor to play video games. Twelve wireless EMG sensors (Delsys Trigno Avanti & Avanti Mini), sampled at 4370 Hz, were placed bilaterally over the muscle belly of the sternocleidomastoid, rectus femoris, tibialis anterior, medial gastrocnemius, soleus, and flexor hallucis brevis muscles. MEPs, startle response times (indicative of reticulospinal tract gain), and F-wave persistence and amplitudes were used to characterize changes in excitability within their respective neural tracts following each condition. This study validates a robust framework for quantifying short-term changes in neural excitability of the cortico-reticulo-spinal circuits in able-bodied individuals by targeting lower limb muscles. The findings of this research will enable future investigations into neural plasticity in individuals with SCI undergoing SCS-assisted neurorehabilitation.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.09/XX74

Topic: I.08. Methods to Modulate Neural Activity

Support: NSF CAREER Award 1845348

Title: Neuronal Outcomes of Different Coil Configurations in Cerebellar Transcranial Magnetic Stimulation: A Computational Study

Authors: *X. ZHANG[1], R. HANCOCK[2], S. SANTANIELLO[1];
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Abstract: The cerebellum is a common target of transcranial magnetic stimulation (TMS) for studying various brain processes and diseases. However, there has been insufficient evidence to support coil type selection, and empirical methods of coil placement, which are based on fiducial markers and do not specifically target the cerebellar region of interest, contribute to variability and suboptimality in outcomes. To tackle these issues and provide quantitative predictions on the neuronal effects under different coil types and placements, we used a previously developed multi-scale pipeline to place a variety of coil types (i.e., MagStim D70 and DCC; MagVenture DB80; Deymed 120BFV) across 28 targets (i.e., a 7×3 grid across the lateral cerebellum along with optimized positions for targeting lobules from V to VIII) on the BigBrain atlas [1, 2], which provides a highly precise reconstruction of the cerebellar cortical surface (average mesh resolution: 126 μm) and enables accurate estimation of the locations and orientations of Purkinje cells [3]. For each of the 112 setups, we predicted the corresponding local activation of Purkinje cells in each lobule and systematically compared the potential effects on the major functional areas usually explored via TMS. Altogether, our study supports identification of the most effective coil setup for targeting the desired cerebellar target and offers guidance for more precise and effective cerebellar TMS studies.
[1]Amunts K, et al. Science 2013;340(6139):1472-5.
[2]Xiao Y et al. Scientific Data 2019;6(1):210.
[3]Zheng J et al. The Cerebellum 2023;22(2):249-60.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.10/XX75

Topic: I.08. Methods to Modulate Neural Activity

Title: Pattern of synchronization between nucleus basalis of Meynert and its cortical targets helps to choose DBS parameters

Authors: *E. LEVICHKINA[1], X. WU[2], L. WESTON[2], T. VIDYASAGAR[1], **C. FRENCH**[3];
[1]Optometry and Vision Sci., [2]Med., [3]Florey Dept. of Neurosci. & Mental Hlth., The Univ. of Melbourne, Parkville, Australia

Abstract: Deep brain stimulation (DBS) effectively prevents motor dysfunctions in Parkinson disease but whether it can alleviate cognitive decline co-occurring with PD (Lewy body dementia) is unknown. Several clinical attempts to use DBS for that purpose reported inconclusive effects. At the same time, DBS experiments in rodents focussed on stimulating nucleus basalis of Meynert (NB) largely resulted in cognitive improvement. While tonic

stimulation was used in clinical studies, the effective stimulation in animal studies is known to be intermittent which includes both low and high frequencies. We hypothesized that communication between NB and cortex involves frequencies in both delta-theta and gamma ranges, making nested frequency patterns potentially more effective. In addition, human clinical studies opted for tonic stimulation across the sleep-wake cycle. We also hypothesized that NB stimulation during sleep can lead to sleep disturbances.
We studied preferred frequencies of neuronal synchronization within NB as well as between NB and its cortical targets in B6 mice (N=6, age 4-6 month) by recording neuronal spiking and local field potentials (LFP) from 2 NB and 4 cortical sites simultaneously across multiple sleep-wake cycles (115 NB cells and 210 cortical cells). Spike-field coherence (SFC) between NB cells and NB LFP revealed natural synchronization tendencies of NB - all animals demonstrated significant SFC at delta-theta range and multiple gamma peaks, largely similar in sleep and wakefulness with higher low frequency SFC in slow wave sleep (SFC > 95% jackknife confidence interval at frequency range > 2*bandwidth). SFC between cortical cells and NB LFP, which reflects cortical feedback, in all but one animal peaked at low frequencies. We conducted a preliminary study of NB stimulation effects on cortical LFPs across sleep-wake cycles (N animals = 3), and compared nested frequencies (5Hz & gamma <100Hz), random and tonic (20Hz) stimulation types. All types of stimulation lead to a significant decrease in delta activity immediately after the stimulation in all states of vigilance even at the lowest intensity (Wilcoxon $p<0.05$), indicating a potential for sleep disturbance. Only nested frequency pattern induced gamma activation during wakefulness, and prolonged suppression of delta activity was more likely to occur with this pattern as well.
We conclude that communication between NB and cortex occurs at gamma bursts nested within delta-gamma oscillations, and NB stimulation using this pattern can be more effective in supporting wakefulness. However, NB stimulation during sleep may lead to sleep disturbances.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.11/XX76

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01NS123424

Title: Differential effects of medial forebrain bundle stimulation on distinct neural subpopulations and dopamine release in the nucleus accumbens

Authors: A. VISHWANATH[1], A. R. HAMILTON[2], N. C. WEINTRAUB[2], C. J. STOPERA[5], G. M. WINTER[1], M. F. SERNA[6], M. L. HEIEN[3], ***S. L. COWEN**[4];

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Abstract: Dopamine release and neural ensemble activity in the nucleus accumbens (NAc) play crucial roles in reward-guided learning, motivation, and decision making. Electrical deep brain stimulation (DBS) is an important tool for the causal manipulation of neural circuits and the treatment of diseases such as Parkinson's disease. The effects of DBS on neural activity and neuromodulator release are complex and incompletely understood. In addition, traditional DBS utilizes fixed inter-pulse intervals at fixed frequencies. This is potentially sub-optimal as neurons and neural circuits are often responsive to unpredictable input. Therefore, this study investigated how inter-pulse variability of DBS applied to the medial forebrain bundle (MFB), the axon bundle connecting ventral tegmental area to the NAc, impacts single-neuron and neural ensemble activity as well as sub-second patterns of dopamine release. **Methods**: Isoflurane-anesthetized male Sprague-Dawley rats (310-400 g) were implanted with a Neuropixels probe (n = 4 rats) and a carbon-fiber microelectrode for measuring dopamine concentration (fast-scan cyclic voltammetry, FSCV). Both probes targeted the NAc (AP: 1.5, ML: 1.4, DV: >6.2 mm). A bipolar stimulating electrode was placed in the MFB. Ten-second biphasic stimulation trains (~300 µA) with varying inter-pulse statistics (tonic to bursting) and mean frequencies of 10 or 20 Hz were delivered. **Results**: Stimulation reliably increased extracellular NAc dopamine concentration, and the time course of release was strongly correlated with the stimulation sequence. Preliminary analyses of neural ensemble recordings indicate that the effects of stimulation varied by neuronal subtype. During stimulation, regardless of frequency or inter-pulse variability, putative medium spiny neurons (MSNs, n = 138) initially increased firing and returned to baseline in <20 seconds. In contrast, putative fast-spiking interneurons (INs, n = 41) were suppressed during stimulation and exhibited a large rebound in firing at stimulation offset that lasted ~2 seconds. Moreover, IN firing rates remained elevated for >2 minutes following stimulation offset. At the network level, stimulation reduced network sparsity and increased overall population activity for tens of seconds to minutes following stimulation offset. These findings suggest that MFB stimulation produces opposing effects on distinct NAc neuronal subgroups, and these effects can persist for minutes after stimulation offset. Further research will explore sub-second relationships between neural ensemble activity, dopamine release, and inter-pulse variability.

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Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: NIH grant 1R01MH123508-01

Title: An investigation of the effects of transcranial direct current stimulation on the rat somatosensory evoked potential

Authors: *L. CHEN[1,2], B. ASAMOAH[1,2], M. MC LAUGHLIN[1,2];
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Abstract: Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation method that uses scalp electrodes to deliver low-amplitude direct currents (DC) which creates a weak electric field (<1 V/m) in the cortex. Anodic tDCS is believed to have a depolarizing effect, leading to cortical excitation; while cathodic tDCS has a hyperpolarizing effect, leading to cortical inhibition. tDCS is used to boost cognitive and motor function in healthy volunteers and is under investigation as a treatment for many neurological and psychiatric disorders. However, the underlying mechanisms behind tDCS remain poorly understood and a number of recent studies have failed to reproduce some previously reported tDCS effects. One approach to address these issues is to develop animal models that can reproduce tDCS neural effects previously observed in humans. These animal models can then be used to study and understand basic tDCS mechanisms. In 8 male Sprague Dawley rats we implanted a 32-channel silicon probe in the somatosensory cortex to measure evoked potentials (SSEPs) elicited by fore-limb stimulation (0.25Hz, 1mA). A screw electrode was implanted over the somatosensory cortex to deliver DC stimulation (3mins, 0.005 to 0.3 mA). To quantify cortical excitation, we normalized SSEPs during stimulation to SSEPs collected before stimulation. The effect of tDCS on normalized SSEP (nSSEP) amplitude was then analysed using a linear mixed model. We found that anodic tDCS significantly increased nSSEP amplitude (i.e. excitation, p <0.01), while cathodic tDCS significantly decreased nSSEP amplitude (i.e. inhibition, p <0.01). The linear model showed that for every 0.1mA step change in anodic tDCS amplitude, cortical excitability increased by 3%, while for every -0.1mA step change in cathodic tDCS cortical inhibition increased by 3%. We showed that animal models can be developed which reproduce some of the basic tDCS effects, similar to those previously reported in humans. This rat model can now be used to accurately quantify the electric field strengths and determine how this corresponds tDCS electric field strength in humans.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.13/XX78

Topic: I.08. Methods to Modulate Neural Activity

Support: DARPA Grant N65236-19-C-8017

Title: Directional preference of transcranial electrical stimulation of the motor cortex in humans

Authors: *M. FORSSELL[1], V. JAIN[1], M. D. MURPHY[2], J. A. SHULGACH[3], D. Z. TANSEL[1], J. CAO[1], S. REZA[1], Y. GUO[1], M. CHAMANZAR[1], D. M. GRIFFIN[2], G. K. FEDDER[1], D. J. WEBER[4], P. GROVER[1];
[1]Electrical and Computer Engin., [2]Neurosci. Inst., [3]Mechanical Engin., [4]Mechanical Engin. and Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Transcranial electrical stimulation (TES) is a non-invasive neuromodulation technique consisting of injecting electrical currents via electrodes placed on the scalp showing promising clinical applications. Commonly, currents are injected using two electrodes with the anode placed above the region of interest and the cathode at a distant location on the head. It has long been held that external electric fields stimulate neurons more effectively when oriented along the axons that are being stimulated. While this effect has been studied for transcranial *magnetic* stimulation, it has not been rigorously verified for TES. Doing so is important, e.g., in order to optimize high-density (HD) TES. HD-TES has recently gained prominence as an attempt to improve the focus of the fields generated in the brain by using HD electrode montages, with a central anode surrounded by equidistant cathodes. While the resulting E-fields are more confined, these montages typically result in larger E-field components normal to the cortical surface and lower tangential components, compared to the two-electrode montages.
In the present study, we applied pulsed TES (100 μs monophasic pulses of amplitude 65-145 mA) to the motor cortex of awake healthy humans (n=4 participants) while monitoring evoked motor activity in hand flexor and extensor muscles using high-density surface electromyography (EMG). Two stimulation electrodes (1 cm diameter gold cups) separated by 7 cm were used to inject the current. The anode was fixed above the forearm representation of the motor cortex (2 cm medial from C3, determined in previous experiments), while the cathode was moved in 22.5° increments to achieve different orientations of the electric field. We found that the motor evoked potential (MEP) amplitude in the contralateral limb is maximized when the two electrodes are aligned with the medio-lateral (ML) axis, with an angular full-width at half-maximum (FWHM) of 48.5°±8.2°. In one participant, we additionally performed small movements of the anode in 7 mm steps to assess whether the observed change in MEP could be due to shifts in the spatial location of the electric field caused by the changing cathode location. We observed similar changes in MEP amplitudes as a function of the field direction independently of the anode location, confirming that the electric field direction drives the motor response.
The results shown demonstrate that TES of the hand motor area exhibits strong directional selectivity. Since directionality in the motor cortex may be a consequence of the orientation of the central sulcus, the strength of this effect on other brain areas is not known and requires further experimentation.

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Poster

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Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant NS123424-01
NIH Grant GM008804

Title: Varying the inter-pulse interval of electrical brain stimulation in the MFB and mPFC alters the time course of dopamine release

Authors: *A. HAMILTON[1], N. C. WEINTRAUB[1], A. VISHWANATH[2], C. J. STOPERA[3], S. L. COWEN[2], M. L. A. V. HEIEN[1];
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Abstract: Dopamine release in the striatum is crucial for reward-guided learning, decision making, and motor control. Electrical deep brain stimulation (DBS) is used in research and for treating Parkinson's disease. DBS typically uses fixed frequencies and fixed inter-pulse intervals, but previous research has shown that neurons and neural circuits are more responsive to variable inter-pulse intervals, or more burst-like pulses. In this study, we seek to understand the effects of increasing the variability of inter-pulse intervals on downstream dopamine release in the nucleus accumbens (NAc). We also investigated whether these effects differ depending on whether stimulation was applied to the medial forebrain bundle (MFB) or the medial prefrontal cortex (mPFC). MFB stimulation directly activates dopamine axons while the mPFC activates a multi-synaptic circuit that ultimately triggers dopamine release. We hypothesized that increased inter-pulse variability, which appears more 'bursty,' will release the most dopamine in the NAc. **Methods:** Anesthetized (isoflurane), male, Sprague-Dawley rats (310-400 g, n = 5 each stimulation region) were implanted with a carbon-fiber microelectrode in the NAc to measure extracellular dopamine concentration at a sub-second resolution using fast-scan cyclic voltammetry. A bipolar stimulating electrode was placed in the MFB or mPFC. Stimulation trains lasted 10 seconds, were generated with differing degrees of inter-pulse variability, and constrained to have an average frequency of 10 Hz or 20 Hz. Local variance (Shinomoto et al. 2003) quantified variability in the inter-pulse intervals. **Results:** Data indicate that increasing stimulation frequency in the MFB increases dopamine release. In the mPFC, dopamine release did not significantly increase when the stimulation frequency increased. Conversely, pulse variability caused opposite trends in the MFB and mPFC as a result of increasing local variance. We observed that increasing local variance in the MFB increased dopamine release while increasing variance of mPFC stimulation evoked less release than fixed inter-pulse interval sequences. The time course of dopamine release followed the time course of variable stimulation sequences more closely when the MFB was stimulated relative to the mPFC. This was further supported by the observation that correlations between MFB stimulation and dopamine release were highest when time was binned using 200 ms intervals while correlations between mPFC and dopamine release peaked when 600 ms intervals were used. These results enhance the understanding of inter-pulse variability and its effect on the time course of dopamine release.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.15/XX80

Topic: I.08. Methods to Modulate Neural Activity

Title: Different direct electrical stimulation paradigms to upregulate and downregulate low-frequency (7-12 Hz) rhythms in human cerebral cortex

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Abstract: Neuromodulation is a rapidly growing tool in research and clinical practice, with potential for large impact in both realms. The devices used for interfacing with the brain are becoming increasingly advanced, however the electrical stimulation strategies used to modulate brain activity have not seen the same development. Low frequency oscillations in the alpha and beta range, a prominent attribute of ongoing neural activity, are a frequent target for modulation. Being able to manipulate these rhythms in a patient-specific manner would be extremely useful for the development of brain computer interfaces. Here we have focused on electrical stimulation strategies to either enhance or suppress these rhythms.

Testing was conducted with 4 patients undergoing invasive monitoring for epilepsy, implanted with stereo-EEG electrodes. Monopolar electrical stimulation was delivered to one electrode per patient. A large surface electrode placed on the patient's thigh served as the return. Electrodes were selected based on whether they exhibited prominent low frequency oscillations (7-12Hz). Three of the electrodes were in temporal lobe, and 1 electrodes was in occipital lobe. Pulse trains were comprised of charge-balanced, biphasic, symmetric, cathodal first pulses, with 0.1ms duration per phase delivered at 1mA.

To enhance low frequency oscillations, we delivered pulse trains comprised of short bursts of high frequency (200Hz) pulses delivered at a regular, lower frequency interval. For example, to entrain an oscillation at 8Hz, we delivered a burst of 4 pulses every 125ms for total duration of 1s. Using this strategy, we were able to enhance the power in the 7-12Hz range by 49% on average across the 1s train, without corresponding changes in other low frequency bands (10 trials, 1 subject). Similar effects were seen in 2 other subjects.

To disrupt low frequency oscillations and suppress low frequency power, we delivered a pulse train with irregularly timed pulses. 200 pulses were delivered over a 1 second interval, with the random inter-pulse timing obtained from a Poisson distribution. This paradigm reduced oscillatory power by an average of 32% across the 1s pulse train, without a significant change in power in the 1-6Hz range (15 trials, 1 subject).

These results show the viability of using electrical stimulation to up or down regulate low frequency rhythms in the cerebral cortex. This could be a useful tool for use in future BCI and neuroscientific research.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.16/XX81

Topic: I.08. Methods to Modulate Neural Activity

Title: Precision functional mapping-guided cortical stimulation improves symptoms in treatment-resistant depression

Authors: *R. J. M. HERMOSILLO[1,2], A. SAKR[3], R. JOHNSON[3], T. MADISON[3], K. B. WELDON[1], S. EITING[4,3], S. KÖNIG[3,5], N. ARNOUDSE[3,6,11], S. NELSON[1], M. C. PARK[5,6], O. MIRANDA DOMINGUEZ[7,1], D. P. DARROW[8,11], T. NETOFF[9], D. A. FAIR[1,2,10], Z. NAHAS[3,11,6];
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Abstract: Depression is the leading cause of disability worldwide. Half of these patients have treatment-resistant depression (TRD). Because of the high dimensionality of symptom presentation, numerous models have been proposed to explain patterns of depressive symptoms. These models have focused on large-scale networks that include combinations of the Default Mode Network (DMN), Fronto-Parietal Networks (FPN), the Salience Network (SN), and several other sub-cortical systems related to mood and the limbic system. Thus far, there have been limited efforts in direct cortical stimulation for TRD. Despite its relatively easy access and success in other domains of cortical stimulation, the substantial variability in cortical network topography makes precise targeting of the model systems difficult. New approaches using Precision Functional Mapping (PFM) now allow for such precise localization within individuals and provide an opportunity for personalized targeting for direct cortical stimulation in TRD. Here we report the first case of an individually-targeted Prefrontal Cortical Stimulation (PCS) informed by PFM for TRD. PFM was conducted with both a supervised or unsupervised approach network mapping algorithm based on two 40 minute resting-state functional connectivity runs. Surgical planning leveraged PFM to isolate areas of pathology in the SN (larger relative to controls, $t=-2.93$ $p<0.01$), and DMN (smaller relative to controls, $t=2.39$ $p<0.01$). PFM was also leveraged to carefully plan electrode placement. An 3D model of four multicontact electrodes(Abbott Laboratories) was placed on the 3D pial surface along with the PFM, to simulate final placement targeting SN, DMN, and FP network motifs, consistent with prior models of pathology . A volume image with the desired placements was then used for stereotactic neuronavigation during craniotomy. A follow up CT scan confirmed accurate placement with pre-surgical targets. Proclaim Elite SCS System stimulation system was implanted 4 days later. Stimulation of the right dorsal medial prefrontal cortex provided immediate feelings of joy. Critically, optimization of stimulation parameters showed distinct positive modulation of emotions and attention which was (59% improvement in mood using the

HRSD24 after 17 week follow-up). Our approach establishes PFM-informed PCS targeting as a viable method for modulation of affected networks in TRD as a therapeutic intervention.

Disclosures: **R.J.M. Hermosillo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); R.H. holds a patent for US20230115330A1: Functional magnetic resonance imaging brain mapping and neuromodulation guidance and monitoring. **A. Sakr:** None. **R. Johnson:** None. **T. Madison:** None. **K.B. Weldon:** None. **S. Eiting:** None. **S. König:** None. **N. Arnoudse:** None. **S. Nelson:** None. **M.C. Park:** None. **O. Miranda Dominguez:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); O.M.D. is a co-inventor of the FIRMM Technology #2198, FIRMM: Real time monitoring and prediction of motion in MRI scans, exclusively licensed to Turing Medical Inc.), O.M.D. is a co-patent holder of US20230115330A1: Functional magnetic resonance imaging brain mapping and neuromodulation guidance and monitoring based thereon. **D.P. Darrow:** None. **T. Netoff:** None. **D.A. Fair:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); D.F. is a co-inventors of the FIRMM Technology #2198 by Turing Medical Inc., D.F. is a co-patent holder of US20230115330A1: Functional magnetic resonance imaging brain mapping and neuromodulation guidance and monitoring based thereon. **Z. Nahas:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.17/XX82

Topic: I.08. Methods to Modulate Neural Activity

Support: Commonwealth Cyber Initiative Central Virginia Node Grant # FP00010500.:

Title: Soft Magnetic Material Cores in Transcranial Magnetic Stimulation Coils and Assessing the Influence of Varying Core Shapes on Generated Magnetic Field in Small Animals

Authors: M. TASHLI[1], G. WEISTROFFER[2], A. MHASKAR[1], D. KUMBHARE[3], M. BARON[2], ***R. L. HADIMANI**[1,4];
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Abstract: Transcranial magnetic stimulation (TMS) is a safe, effective and non-invasive treatment for several psychiatric and neurological disorders. TMS is FDA approved treatment for depression and obsessive-compulsive disorders [1]-[3]. Lately, there has been a research surge in utilizing this novel technology in treating other neurological and psychiatric ailments. The application of TMS on other several neurological disorders requires the magnetic flux density

and electrical field to be focal and targeted to a small region in the brain [4]. Multiple coil designs have been introduced in the literature to improve the focality of TMS coils, whereas, slight few numbers of these designs have adapted soft magnetic materials as coil cores to focus the magnetic flux. In this study, some new core configurations will be tested in Finite Element Simulations on a rat head model while some of them will be tested experimentally.Finite element analysis of the rat head model is done using Sim4life and Ansys Maxwell while investigating variations associated with changing the coil core material and design. Materials proposed for the analysis in this study include but not limited to Iron Cobalt Vanadium alloy (FeCoV), Iron (AISI 1010 Carbon Steel) and Manganese Zinc ferrites (MnZn Ferrites). Simulation results are presented below in (Fig. 1), comparing the generated magnetic field distribution of 4 types of cores. Furthermore, a novel parabolic coil design with a sharpened tip was developed to concentrate the E-Field to the targeted region in the rat head model without stimulating adjacent regions (Fig. 2) [5]. Further analysis will be done for this novel coil.Acknowledgment: Authors acknowledge Commonwealth Cyber Initiative Central Virginia Node Grant # FP00010500.:
References:[1]M. S. George *et al.*, *Arch. Gen. Psychiatry*, vol. 67, no. 5, pp. 507-516, May 2010 [2]D. W. Dodick *et al.*, *Headache J. Head Face Pain*, vol. 50, no. 7, pp. 1153-1163, Jul. 2010, [3]O. of the Commissioner, "FDA permits marketing of transcranial magnetic stimulation for treatment of obsessive compulsive disorder," *FDA*, Mar. 24, 2020. [4]J. Selvaraj *et al.*, *IEEE Trans. Magn.*, vol. 54, no. 11, pp. 1-5, Nov. 2018, doi: 10.1109/TMAG.2018.2846521.[5]M. Tashli *et al.*, *AIP Adv.*, vol. 13, no. 2, p. 025319, Feb. 2023,

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.18/XX83

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01NS110893
APP1187416

Title: Direct current onset excitation controlled through electrode positioning

Authors: *Y. DU[1], C. CHENG[1], G. FRIDMAN[2];
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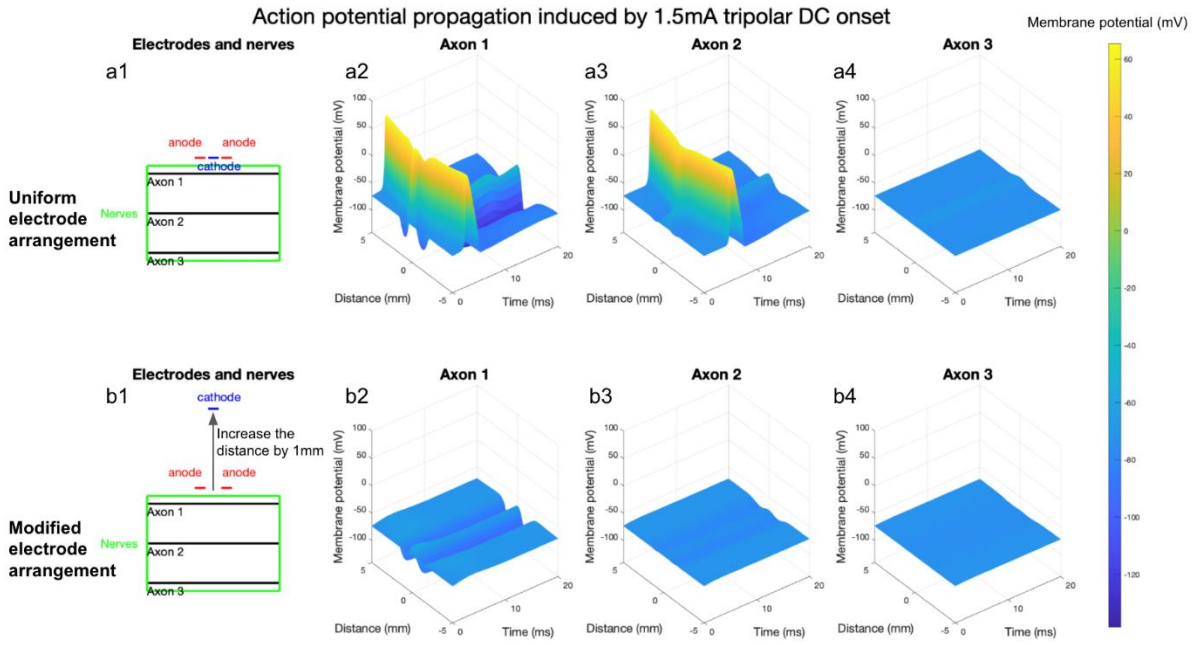
Abstract: Direct current (DC) delivered to a nerve can block action potential (AP) propagation in individual axons. This block has been shown to be useful by us and others, to control chronic peripheral nociceptive pain. The onset of DC however evokes undesired APs. These are commonly controlled by lengthening or ramping up the duration of the DC onset. This tendency to evoke APs also depends on the distance of the axon to the stimulation site. The conventional

technique to control neural excitation is to use tripolar stimulation. The current from the side anodes that hyperpolarize the neuron is driven to the center cathode to prevent depolarizing the neuron further downstream of the electrode site. While this technique has been used to control the neural response over a longer duration, it has been less effective in suppressing undesired excitation for DC onset. Here we hypothesize that the main origin of undesired APs is at the center of the stimulation site in response to strong cathodic depolarization. The high amplitude of cathodic current causes AP to form in the center, while the hyperpolarized sidelobes due to the anodes are too weak to suppress it from propagating. In our computational model, we demonstrated this effect for three axons positioned at different distances from the stimulation site (a1, a2, a3, a4). Our solution is to move the cathode further away from the nerve to reduce the depolarization effect of the cathodic electrode. Panels b1, b2, b3, and b4 demonstrate the effect and the reduction of the undesired AP formation in the center. With increased the cathode distance by 1mm in the model, and the threshold of DC onset neural excitation increased from 0.23 mA to 1.59 mA for axon 1, from 1.35 mA to 5.85 mA for axon 2, and from 4.10 mA to 9.75 mA for axon 3.



Disclosures: **Y. Du:** None. **C. Cheng:** None. **G. Fridman:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.19/XX84

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01NS110893
Australia NHMRC Ideas Grant APP1187416

Title: Freeform Stimulator (FS): Stepper Motor-Integrated Implant Design for Non-Pulsatile Arbitrary Waveform Neuromodulation

Authors: *A. CHENG[1], Y. XU[1], G. FRIDMAN[2];
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Abstract: Freeform Stimulator (FS): Stepper motor-integrated implant design for non-pulsatile arbitrary waveform neuromodulation**Authors**Alexandra Cheng[1], Yangsheng Xu[2], Gene Fridman[1,21]Johns Hopkins University, Department of Biomedical Engineering, Baltimore, USA[2]Johns Hopkins Medicine, Department of Otolaryngology, Baltimore, USA**Disclosure**Research was funded by NIH R01NS110893 and Australia NHMRC Ideas Grant APP1187416.**Abstract**In contrast to conventional pulsatile stimulation that evokes action potentials in phasewith pulse presentations, ionic direct current (iDC) or low frequency neuromodulationis capable of axonal excitation, inhibition, and synaptic sensitization. Despite itsversatility, iDC cannot be delivered safely via metal electrodes for safety concerns suchas pH changes, electrolysis, and corrosion. Our lab and others published extensively onthe applications of iDC neuromodulation for improving vestibular implants, blockingpain in the peripheral nerve, and modulating cortical processing.[1] We previouslyproposed several designs of a microfluidic device that rectifies electrical pulses deliveredto metal electrodes into an ionic DC current delivered to the neurons. The architectureallows each electrode to alternate between charging and driving current to the tissue orbeing discharged to avoid electrochemical reactions. The main reliability concern inthese designs has been shape memory alloy actuation due to its thermal and structuralinstability. In this work, we propose a novel design that uses a miniature stepper motorinstead of shape memory alloy as the actuator. The motor rotates an inner cylinderhousing the two hydrogel-coated metal electrodes within another concentric outercylinder. As the electrodes encounter the hydrogel reservoirs on the wall of the outercylinder, a gel bridge is created to allow ionic current to pass through. This rotatingmechanism greatly improves the reliability and efficiency of the device compared withprevious generations.[1]F. P. Aplin and G. Y. Fridman, “Implantable Direct Current Neural Modulation: Theory,Feasibility, and Efficacy,” Front Neurosci, vol. 13, Apr. 2019, doi*10.3389/fnins.2019.00379

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.20/XX85

Topic: I.08. Methods to Modulate Neural Activity

Support: Johns Hopkins Center for Psychedelic and Consciousness Research
Alexandra Cohen Foundation
Tim Ferriss, Matt Mullengweg, Craig Nerenberg, and Blake Mycoskie

Title: Investigating Test-Retest Reliability of TMS-Evoked Potentials (TEPs): Exploring TMS Protocols Across Distinct Target Sites

Authors: *C. SAYALI[1], D. JARO[1], G. LOFLAND[1], S. DARCY[1], E. WEISMAN[1], F. S. BARRETT[2];
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Abstract: Concurrent Electroencephalography (EEG) and Transcranial Magnetic Stimulation (TMS) has been recently utilized to assess the effects of various treatments on brain function, yet the test-retest reliability of TMS-evoked potentials (TEPs) remains inadequately understood. Test-retest reliability is crucial for evaluating the magnitude of effects of a given intervention on an outcome measure, particularly in TMS studies as intrinsic neural fluctuations and uncontrolled extrinsic factors can contribute to variability in TEPs across sessions, impacting the reliability of TEP-based outcomes. While previous research has focused mainly on motor evoked potentials (MEPs) and standardized TMS target locations, limited studies have assessed the test-retest reliability of TEPs and generalizability to other stimulation protocols and target sites. This study aims to fill this gap. Neurologically and clinically healthy participants (n=11; data collection is ongoing) underwent magnetic resonance imaging to obtain anatomical and resting-state functional brain images for neuronavigation-guided TMS. Resting-state data were separately decomposed into canonical network maps for each participant using independent components analysis (ICA). Two concurrent EEG and TMS sessions were then completed, with at least one week between sessions. In each session, TEPs were generated across distinct brain regions (the motor cortex, DLPFC as a node of the fronto-parietal task control network, and angular gyrus as a node of the default mode network) using literature-derived target coordinates as well as individualized target coordinates based on ICA-derived resting-state networks. TEPs were compared between literature-derived and individualized coordinates, and between a single pulse TMS protocol and paired-pulse TMS protocols with interstimulus intervals of 3ms (to stimulate cortical inhibition) and 11ms (to stimulate cortical excitation) at each coordinate. Preliminary results showed that concordance correlation coefficients (CCCs) for all protocols were moderate (0.34 - 0.52) with single-pulse protocols showing the greatest reproducibility. Additionally there was no significant difference in CCCs between individualized versus standardized targets (individualized: 0.43 [0.19 0.61]; standardized: 0.51 [0.29 0.68]). By investigating the test-retest reliability of TEP measurements across various brain regions and TMS protocols, this study contributes to the understanding of the reliability of TMS measurements, which may advance our understanding of the underlying neurophysiological processes associated with TEPs.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.21/XX86

Topic: I.08. Methods to Modulate Neural Activity

Support: EU POWERMAPS 114618

Title: Terminating ECoG high-gamma activity increases the effectiveness of ECS during speech production

Authors: *C. KAPELLER[1], K. KAMADA[3], M. MOHAMMADPOUR[1], K. MAYR[1], **C. GUGER**[2];
[2]g.tec medical engineering GmbH, [1]g.tec medical engineering GmbH, Schiedlberg, Austria; [3]Megumino Hosp., Eniwa, Japan

Abstract: Electrical cortical stimulation (ECS) of the brain can change our behavior and the way how our brain works. This phenomenon has been demonstrated by observing stimulation-related symptoms such as involuntary movements, visual illusions, or transient aphasia while stimulating the motor, visual, or language cortices. It turned out that the resection of those areas often led to postsurgical function deficits, and, thus, ECS is a valuable method for pre- or peri-operative functional mapping. Especially for language mapping, where ECS became the gold standard technique for preserving the ability to speak. Stimulation protocols during a language task like the Boston naming test have been well established, but are mainly created based on empirical observations and greatly differ from patient to patient. Hence, it is important to better understand the causality of the applied stimulation settings and the behavioral symptoms. An additional biomarker, broadband high-gamma activity (HGA) in the electrocorticography (ECoG), was demonstrated to reflect language neural activity with a great spatial resolution. The aim of this study was to determine whether the onset time of ECS during a naming task affects the frequency of symptoms and, if so, how it aligns with the HGA time course. Two epilepsy patients of the Megumino Hospital in Japan gave informed consent to participate in this extension of the routine clinical ECS language mapping prior to a resective brain surgery. A picture naming task was performed without ECS to observe task-related HGA. The clinical routine ECS revealed locations where stimulation with 5-7mA elicited transient aphasia, paranomia, or paraphasia. Thus, the location with the strongest HGA was selected as the stimulation target for variable ECS onsets between 0.35 and 1s after picture onset. Stimulation at 50Hz lasted for 1s and each trial was labeled either with ‘no symptom’ if the speech was not disturbed, or ‘symptom’ if any of the aforementioned symptoms arose. The HGA reached a top of 5.44 and 4.72 z-scores at 684 and 454ms, and the full-width-half-maximum was 383-955 and 333-764ms for P1 and P2, respectively. The ECS symptom rate of P1 and P2 was 92 and 47% before the HGA peak and reduced to 37 and 13% afterward. The ECS symptoms reduced once the HGA reached its top, indicating a strong relationship between speech production, HGA, and the effectiveness of ECS. Furthermore, it shows that patients that respond faster require earlier ECS compared to slower ones. Such personalized stimulation protocols can make functional

mapping more efficient by reducing the time of stimulation, which can improve time-critical mapping during awake craniotomies.

Disclosures: **C. Kapeller:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **K. Kamada:** None. **M. Mohammadpour:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **K. Mayr:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **C. Guger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec medical engineering GmbH.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.22/XX87

Topic: I.08. Methods to Modulate Neural Activity

Support: JST Moonshot R&D (JPMJMS2012)

Title: The influence of stimulus pulse duration on corticospinal excitability in neuromuscular electrical stimulation

Authors: *K. HAYASHIDA[1], J. USHIBA[2], M. TAKEMI[1];
[1]Grad. Sch. of Sci. and Technol., [2]Fac. of Sci. and Technol., Keio Univ., Yokohama, Japan

Abstract: Neuromuscular electrical stimulation (NMES) is a neurorehabilitative method utilized for improving motor function in individuals with post-stroke paralysis. This method involves the application of electrical currents to the skin, which depolarize sensory nerves underlying the stimulating electrodes. NMES has been shown to increase the excitability of corticospinal projections in a frequency- and duration-specific manner. However, the specific impact of pulse width on this process remains unclear. This study aimed to investigate the effect of NMES pulse width on corticospinal excitability. Twenty-four healthy subjects were recruited for this study. Robotic transcranial magnetic stimulation was used to assess corticospinal excitability before and after 40 min of median nerve stimulation at a stimulation frequency of 100 Hz. The pulse widths of 0.3 ms and 1 ms were selected for the experiment. Motor-evoked potential amplitudes of the abductor pollicis brevis muscle were fitted to a stimulus-response curve (SRC) to estimate the dependent variables reflecting neurotransmission efficiency. The results showed that NMES could transiently increase corticospinal excitability regardless of the pulse width. An ANOVA demonstrated a significant interaction between the presence or absence of NMES application and the time course after NMES for the SRC-dependent variables reflecting neurotransmitter efficiency ($F(3,66) = 3.403$, $p = 0.023$) but not for the factors NMES application, time after NMES, and the pulse width ($F(3,66) = 2.62$, $p = 0.058$). Post-hoc pairwise comparisons indicated a difference in neurotransmitter efficiency between immediately after 40 min of NMES and after 40 min of Rest ($t(23) = 3.156$, $p = 0.044$). Furthermore, although ANOVA did not reveal

significant interaction with the factor pulse width, there was a marginally large difference in the percentage increase in neurotransmitter efficiency immediately after NMES application for a pulse width of 1 ms compared to 0.3 ms (1 ms: 156% increase, 0.3 ms: 114% increase). Consistent with previous findings, our results demonstrated that NMES is capable of enhancing corticospinal excitability. However, the differential impact of NMES on corticospinal excitability between pulse widths of 1 ms, which are believed to effectively induce afferent volleys, and 0.3 ms, which is less painful, was not evident. These findings suggest that NMES utilizing less painful parameters could be used as a plasticity-inducing protocol in clinical practice.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

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Program #/Poster #: PSTR312.23/XX88

Topic: I.08. Methods to Modulate Neural Activity

Title: Topography heat maps to visualize the source of EEG-based biomarkers for deep brain stimulation in Parkinson’s disease

Authors: J. PEETERS[1], T. DEMBEK[2], A. BOOGERS[1], T. VAN BOGAERT[1], R. GRANSIER[1], J. WOUTERS[1], B. NUTTIN[1], ***M. MC LAUGHLIN**[1];
[1]Neurosci., KU Leuven, Leuven, Belgium; [2]Fac. of Med., Univ. of Cologne, Cologne, Germany

Abstract: Subthalamic deep brain stimulation (STN-DBS) is a well-established therapy to treat Parkinson’s disease (PD). The wide parameter space and time constraints can make the programming of patients challenging. One solution could be to use EEG-based evoked potentials (EP) to guide programming. Previously, we have investigated EEG-based evoked potentials (EPs) as a biomarker to guide programming. We found that a 3-millisecond peak (P3) was strongest in contacts closest to motor STN and could predict the best DBS-contact configuration. Together with evidence in literature, these results led to the hypothesis that P3 may be caused by hyperdirect pathway (HDP) activation. Alternatively, we found that a 10-millisecond peak (P10) was related to substantia nigra (SNr)-related side effects. Here, we investigated in the scalp location where P3 and P10 are strongest by calculating EEG-based topographic heat maps. Stimulation was delivered at 10Hz for 50s at each contact of a directional lead, while EPs were recorded using 64-channel EEG. Next, right hemispheric stimulations were transformed to the left hemisphere and all EPs were averaged across hemispheres for each EEG channel resulting in an average 64-channel dataset. Lastly, topographic heat maps were calculated at the latency for P3, P10, and the stimulation artifact.Data from 12 hemispheres were grouped for P3 and the stimulation artifact, and from 13 hemispheres for P10.

The topographic heat map for P3 shows strongest activity in the primary motor and premotor cortex ipsilateral of stimulation, while the through of activity was observed in the parietal cortex ipsilateral of stimulation. The topographic heat map for P10 shows strongest activity in the prefrontal cortex ipsilateral of stimulation and lowest activity in the occipital area. As a control, the topographic heat map for the artifact represents a deep source.
The P3 topography strengthens the hypothesis that P3 may be caused by HDP activation. Next, the P10 topography supports the previously published data that P10 is probably related to SNr activity as a SNr-to-prefrontal connection has been described in literature. These results strengthen our previous hypotheses that P3 and P10 are important biomarkers to facilitate the DBS programming of PD patients.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.24/XX89

Topic: I.08. Methods to Modulate Neural Activity

Title: A machine learning-based approach to select parameters for safe electrical neural stimulation

Authors: Y. LI[1], R. FREDERICK[2], D. GEORGE[1], S. COGAN[1], J. J. PANCRAZIO[3], L. BLERIS[3], ***A. HERNANDEZ-REYNOSO**[1];
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Abstract: Stimulation of the nervous system can be used to restore function after neurological injury or disease. The safety of delivering currents to neural tissues depends on the stimulation parameters. The Shannon equation is an accepted linear model to separate damaging from non-damaging parameters based on log10 values of charge and charge density. However, this equation was developed based on a small dataset for cortical macroelectrodes and may not accurately predict outcomes beyond this limited space. Here, we report on a machine learning approach to more reliably predict stimulation-induced tissue damage in response to different parameters.A literature search was conducted using keywords including “neuromodulation”, “damage”, “safe”, “neural interfaces”, as well as literature cited in previous neural stimulation reviews. Stimulation parameters were extracted from each publication. Tissue responses were either reported by the included studies or scored by two blinded investigators as damaging or non-damaging. Then, we calculated the accuracy of the Shannon equation on the entries of this database. Subsequently, we used ordinal encoding and Random Forest for feature selection and then developed a machine learning model based on One-Hot encoding and Random Forest classification. Finally, we compared these results against the accuracy of the Shannon

equation.We compiled a database with 387 unique stimulation parameters collected from 58 studies. There was a discrepancy between the two investigators scores in only 3% of database entries. Tissue response scores in the database were balanced showing 195 (51%) entries as non-damaging and 190 (49%) as damaging. The features selected were pulse waveform, geometric surface area, pulse width, frequency, pulse amplitude, charge per phase, charge density, current density, stimulation train duration, daily stimulation duration received, daily number of pulses delivered and daily accumulated charge. The Shannon equation yielded an accuracy of 63.9% using a k = 1.79. In contrast, the random forest algorithm was able to robustly predict whether a stimulation parameter was damaging or non-damaging with an accuracy of 89.6%.The use of this model for prediction of stimulation parameters on neural tissue outcomes can facilitate informed decision-making in selection of neuromodulation parameters for research and clinical practice. This is the most comprehensive database to date for stimulation parameters and neural tissue outcomes and the results indicate high generalization to new parameter combinations. Future work will further validate this model against novel electrode designs and stimulation parameters.

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Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

Time: Monday, November 13, 2023, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR312.25/XX90

Topic: I.08. Methods to Modulate Neural Activity

Support: Marie Sklodowska-Curie Fellowship 101030486

Title: Identification of controller parameters for closed-loop deep brain stimulation

Authors: *J. ORLOWSKI, M. LOWERY;
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Abstract: Deep Brain Stimulation (DBS) is a widely used treatment for Parkinson's disease (PD). It has proven effective in reducing the symptoms of PD, however, conventional DBS treatments are not always sufficient to meet the needs of patients in the long-term. Adaptive DBS (aDBS) is an emerging technology that improves upon conventional DBS by automatically adjusting the stimulus parameters in response to the patient's condition in real-time.
In recent years, the majority of the proposed aDBS solutions have utilized the magnitude of beta (13-30 Hz) oscillations as a biomarker with which to adjust either stimulation amplitude or frequency. Proportional-Integral-Derivative (PID) control is a well-established approach for controlling a wide range of systems and is effective even when the systems are very complex, have unknown internal dynamics and are subject to noise.
While powerful and responsive, PID controllers need to be tuned to realize their potential. A

range of techniques exist to help select the controller parameters; however, many of them require precise knowledge of the internal dynamics of the controlled system and are poorly suited to situations where the underlying dynamics change over time as is the case with neural systems e.g., due to diurnal variation of symptoms or the disease progression.
In this study we examine the use of iterative feedback tuning (IFT) to identify and update DBS controller parameters in a way that minimizes a specified objective function using only data recorded during controller's operation. An IFT-tuned PI controller is applied within a computational model of cortico-basal ganglia loop to suppress pathological beta activity in subthalamic nucleus local field potentials. We run the simulations for a range of initial controller parameters through multiple iterations of the IFT algorithm. We show that the resulting update of the controller parameters results in a reduction in the value of the objective function compared to the initial condition.
The results demonstrate a method for automatic identification and updating of controller parameters for use in closed-loop neuromodulation systems including DBS, with potential for further development and optimization of aDBS technology. In addition, the testing framework developed provides a means with which to compare the efficacy and efficiency of novel aDBS algorithms.

Disclosures: J. Orlowski: None. **M. Lowery:** None.

Poster

PSTR312. Parameter Searching for Neural Stimulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR312.26/XX91

Topic: I.08. Methods to Modulate Neural Activity

Support: Medical Research Council grant MC_UU_00003/1

Title: How to optimally stimulate to modulate phase-amplitude coupling?

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Abstract: Phase-amplitude coupling (PAC), which involves the coupling of the phase of slower brain oscillations with faster oscillations, plays a significant role in brain activity and has been implicated in various neurological disorders. For example, in Parkinson's disease, PAC between the phase of the beta rhythm (13-30 Hz) and the amplitude of the gamma rhythm (50-200 Hz) in the motor cortex is exaggerated compared to patients with dystonia and humans without a movement disorder. Conversely, in patients with Alzheimer's disease, PAC between the theta (4-8 Hz) and gamma rhythms is diminished compared to healthy controls. Modulating PAC levels (i.e. reducing or enhancing PAC) using brain stimulation could therefore open new therapeutic avenues. However, while it has been previously reported that phase-locked stimulation can increase PAC in the motor cortex, it is unclear what the optimal stimulation strategy to modulate

PAC might be. Here, we provide a theoretical framework to narrow down the experimental optimisation of stimulation aimed at modulating PAC, which would otherwise rely on trial and error. We make analytical predictions using a Stuart-Landau model, and confirm these predictions in a more realistic model of coupled neural populations, the Wilson-Cowan model. Our framework specifies the critical Fourier coefficients of the stimulation waveform which should be tuned to optimally modulate PAC. Depending on the impact of stimulation on the mean-field, these components may include the slow frequency, the fast frequency, combinations of these, as well as their harmonics. We show that the optimal balance of energy between these Fourier components depends on the relative strength of the endogenous slow and fast rhythms. Furthermore, we demonstrate that phase locking the stimulation to the slow rhythm is only necessary if stimulation is weak and overriding the existing PAC is detrimental. Together, our theoretical framework lays the foundation for guiding the development of innovative and more effective brain stimulation aimed at modulating PAC for therapeutic benefit.

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